Insulin Resistance: A biomarker of Allostatic load: Implications for Premature Cognitive Aging

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What is Allostatic Load?

• “Allostatic load (AL) and overload are terms that represent degrees of severity of a cumulative effect of stress on the body and brain, and that acknowledge that the same mediators, when overused and dysregulated relative to each other, can be at the root of stress pathophysiology.”

• AL can lead to mood disorders and dementia, among other conditions

What is Insulin Resistance (IR)?

- Reduced responsiveness of insulin-signaling pathways
- Risk factor for type II diabetes and dementia
- Reversible

Insulin resistance, an unmasked culprit in depressive disorders: Promises for interventions

Kathleen Watson, Carla Nasca, Linn Aasly, Bruce McEwen, Natalie Rasgon

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- IR is a pathological proinflammatory state underlying neuropsychiatric and somatic diseases.
- IR is part of a cascade of allostatic load, which is mediated in the periphery and CNS.
- PPAR-γ receptors, glutamate, cortisol are among mediators of peripheral and central crosstalk underlying IR.
How Does IR Affect the Brain?

• Hippocampus:
  • Interconnected brain region implicated in many functions including episodic memory, regulating depression and anxiety, and visuospatial navigation

• IR may have adverse effects on a dendritic spine and synapse formation in the hippocampus
  • Structurally and functionally
Hippocampal volume reduction is associated with direct measure of insulin resistance in adults

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• Cohort:
  • N=104
  • Ages: 23-61
  • Overweight and obese adults (BMI between 25-35)

• Data collected:
  • Steady state plasma glucose (SSPG) test
  • Imaging: structural MRI (sMRI) for hippocampal volume
  • Other variables: fasting insulin, glucose, leptin, BMI, adiposity

• Statistics:
  • K-means clustering: unsupervised machine learning method
  • Used variables listed above to identify two different clusters of individuals
IR Associated with Smaller Hippocampal Volume

- K-means identified two clusters
- Adiposity, insulin resistance and compromised structural hippocampal integrity behave as a composite phenotype
- Female sex as risk factor for this phenotype

**Table 2**

Sociodemographic and metabolic characteristics of the 2-cluster solution.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cluster 1 (N=49)</th>
<th>Cluster 2 (N=65)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, N (%)</td>
<td>20 (42 %)</td>
<td>52 (79 %)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age, years</td>
<td>39.8 (8.5)</td>
<td>37.6 (8.6)</td>
<td>0.18</td>
</tr>
<tr>
<td>White, N (%)</td>
<td>30 (61 %)</td>
<td>30 (46 %)</td>
<td></td>
</tr>
<tr>
<td>Black, N (%)</td>
<td>17 (35 %)</td>
<td>18 (28 %)</td>
<td>0.11</td>
</tr>
<tr>
<td>Other race/ethnicity, N (%)</td>
<td>2 (4 %)</td>
<td>17 (26 %)</td>
<td></td>
</tr>
<tr>
<td>Year of education</td>
<td>18.33 (4.44)</td>
<td>16.48 (4.38)</td>
<td>0.03</td>
</tr>
<tr>
<td>Waist circumference, m</td>
<td>0.96 (0.08)</td>
<td>0.99 (0.12)</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>27.9 (2.5)</td>
<td>30.5 (4.6)</td>
<td><strong>0.0002</strong></td>
</tr>
<tr>
<td>Normal weight, N (%)</td>
<td>7 (14 %)</td>
<td>7 (11 %)</td>
<td></td>
</tr>
<tr>
<td>Overweight, N (%)</td>
<td>34 (69 %)</td>
<td>25 (38 %)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Obese, N (%)</td>
<td>8 (16 %)</td>
<td>33 (51 %)</td>
<td></td>
</tr>
<tr>
<td>SSPG, mg/dL</td>
<td>123 (61)</td>
<td>156 (70)</td>
<td><strong>0.008</strong></td>
</tr>
<tr>
<td>Fasting insulin, mU/L</td>
<td>9.0 (3.8)</td>
<td>10.8 (7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>89 (8)</td>
<td>92 (10)</td>
<td>0.07</td>
</tr>
<tr>
<td>Leptin, µg/L</td>
<td>21.7 (17.9)</td>
<td>44.5 (30.4)</td>
<td>1.70E-06</td>
</tr>
<tr>
<td>Cortisol, µg/dL</td>
<td>9.0 (4.7)</td>
<td>9.0 (4.5)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Continuous data are shown as mean (standard deviation) and categorical data as number (percentage); BMI—body mass index; SSPG—steady-state plasma glucose; Bold font indicates significant results at P<0.05 with False Discovery rate correction.

**Figure:** Violin plots depicting cluster differences in total hippocampal volume
• Cohort same as previous study
• Data:
  • Hippocampal connectivity data measured from functional MRI (fMRI)
    • Cohesiveness vs integration
  • Wechsler Abbreviated Scale of Intelligence (WASI) – general measure of cognition
  • Digit Symbol Pairing and Digit Symbol Free Recall – episodic memory
• Statistics:
  • K-means clustering
IR associated with lower cohesiveness in hippocampus

- K-means clustering identified two groups
- Lower cohesiveness and integration in group with greater metabolic deviance
- May be regulated by leptin
- Clusters did not differ by general intellectual ability or episodic memory

*Figure:* Lower functional cohesiveness and integration of the hippocampus in metabolically challenged individuals
Take Home Messages

- Insulin resistance is associated with changes in the brain (both structural and functional) in adults without any psychiatric/somatic illnesses (with exception of overweight/obese)
- Identifying associations early in the life and/or disease course is key
- Insulin resistance is modifiable!
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