Effects of intranasal insulin as adjuvant on fear extinction in healthy humans: a randomized, double-blind, placebo-controlled experimental study

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How to make treatments more effective?

• Use of endogenous hormones and pharmacological agents that enhance extinction learning and memory
  • Cortisol (Soravia et al., 2006, Lass-Hennemann & Michael, 2014; Yehuda et al., 2015)
  • D-cycloserine (Hofmann et al., 2006; Otto et al., 2009)
  • Oxytocin (Acheson et al., 2013)

• Insulin?
  • modulates learning and memory processes (Stockhorst et al., 2004)
Insulin

- Peptide hormone produced in the pancreatic β-cells
- Main function: glucose homeostasis

- Potential to cross the blood-brain barrier → reach the CNS components of the insulin signaling pathway

Hypothalamus
Hippocampus
Amygdala
Cerebellum
Bulbus olfactorius

ENERGY
COGNITION

Intranasal application of Insulin

Insulin crosses the nose mucosa
Diffuses into the cerebrospinal fluid (CSF) through olfactory epithelium
Reaches brain receptors
Enables the study of central insulin under euglycemia (less invasive)

Schlure, C (2013)
Beneficial effects of central insulin on memory processes

- Better memory performance in patients with Alzheimer’s disease and mild cognitive impairment (Freiherr et al., 2013; Claxton et al. 2015)

- Better declarative memory in healthy participants, chronic and one time application (Benedict et al., 2004; Benedict, Kern, Schultes, Born, & Hallischmid, 2008; Hallischmid, Benedict, Schultes, Born, & Kern, 2008; Krug, Benedict, Born, & Hallischmid, 2010)

- Evidence for sex differences in central insulin signaling: greater improvement of memory functions in women (Benedict et al., 2008)
Does intranasal insulin facilitate fear extinction?

Pre-Registered Trial: DRKS-ID
DRKS00010551

- Double-blind, placebo controlled study

- 123 healthy participants
  - Intranasal insulin - 160 I.U.
    - 62 participants (31♀)
  - Placebo - vehicle solution
    - 61 participants (32♀)

- Similar insulin-glucose levels:
  - Food restriction for at least 10 h
  - Controlled for time of day (8h-13h)
Pre-Registered Trial: DRKS-ID
DRKS00010551

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**Fear Potentiated Startle S skin Conductance Response**

<table>
<thead>
<tr>
<th>Time</th>
<th>CS+</th>
<th>CS-</th>
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<tbody>
<tr>
<td>0</td>
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</tbody>
</table>

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Startle
SCR
UCS
Stimulus
CS+/CS-
Neutral face (male/female)

**Acquisition**

Fear Potentiated Startle
Skin Conductance Response

Time < .001
CSType < .001
Time x CSType < .005
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Glucose levels

<table>
<thead>
<tr>
<th>Condition</th>
<th>Arrival</th>
<th>+30 min</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
<td><img src="image3.png" alt="Graph" /></td>
</tr>
<tr>
<td>Placebo</td>
<td><img src="image4.png" alt="Graph" /></td>
<td><img src="image5.png" alt="Graph" /></td>
<td><img src="image6.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

Differential startle response

CS+ - CS-

- Condition p < .05
- Condition*Sex p > .05
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Differential SCR
CS+ - CS-

Differential Skin Conductance Response [T-Scores]

-0.2
-0.1
0.0
0.1
0.2
0.3

Men

Women

-0.2
-0.1
0.0
0.1
0.2

Early Late

Early Late

Time

Insulin Placebo

- Condition, p >.05
- Time*Condition, p >.05
- Time*Condition*Sex, p =.006

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Re-Extinction Learning
Differential Startle

Re-Extinction Startle

Men

Women

- Condition, p >.05
- Time*Condition, p >.05
- Time*Condition*Sex, p =.006
Summary of results and discussion

• Extinction
  • Men and women receiving insulin show enhanced extinction on FPS.
  • Only women receiving insulin show enhanced extinction on SCR (effect only present in early extinction)

• Re-Extinction
  • No insulin effect on FPS
  • Only women in the insulin group show enhanced re-extinction on SCR (effect only present in late re-extinction)

• Intranasal insulin is a promising enhancer of exposure therapy, but sex effects need to be taken into consideration.
Thank you!

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Questions?