Estudi del paper de la dieta en l'aparició de processos neurodegeneratius en models preclínicos

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**Nutrition** is the intake of food, considered in relation to the body’s dietary needs.

- Healthy dietary practices start early in life – breastfeeding fosters healthy growth, reduced obesity in adult life and improves cognitive development.
- Unhealthy diet and lack of physical activity are leading global risks to health.

### Energy Intake vs. Energy Expenditure

- Fat should not exceed ≤ 30% of total energy intake
  - Unsaturated > Saturated
  - ▶️ Trans-Unsaturated

- Sugar intake should be < 10% of total energy intake.
  - Salt < 5 g /day

*Information extracted from the World Health Organization (WHO)*
**Overweight** and **Obesity** are conditions defined as abnormal or excessive fat accumulation that may impair health.

\[
\text{Body Weight Index (BMI)} = \frac{\text{Mass (kg)}}{(\text{Height in meters})^2}
\]

Data from 2016:

- 1.9 billion adults >18 were overweight (25% of the world population)
- >650 million adults were obese (13% of the world adult population)
- Prevalence of obesity tripled between 1975-2016.

*Information extracted from the World Health Organization (WHO)*
Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults

*NCD Risk Factor Collaboration (NCD-RisC)*

**Summary**

**Background** Underweight, overweight, and obesity in childhood and adolescence are associated with adverse health consequences throughout the life-course. Our aim was to estimate worldwide trends in mean body-mass index (BMI) and a comprehensive set of BMI categories that cover underweight to obesity in children and adolescents, and to compare trends with those of adults.
Information extracted from The Lancet issue October 10, 2017
Nutrition and Obesity

“Obesigenic” environment

Restrictive environment

**Obesity Predisposition**

Data extracted from Blundell JE et al., 2005

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>HFD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Weight [g]</td>
<td>401.1 (3.5)</td>
<td>457.7 (11.9)**</td>
</tr>
<tr>
<td>Baseline Glucose [mg/dl]</td>
<td>132.7 (8.3)</td>
<td>157.6 (8.4)</td>
</tr>
<tr>
<td>AUC Glucose [a.u.]</td>
<td>29065.0 (2388.3)</td>
<td>36414.8 (1940.1)*</td>
</tr>
<tr>
<td>Baseline Insulin [µg/l]</td>
<td>3.7 (0.4)</td>
<td>8.3 (0.6)**</td>
</tr>
<tr>
<td>AUC Insulin [a.u.]</td>
<td>663.0 (47.1)</td>
<td>1391.3 (90.2)**</td>
</tr>
<tr>
<td>Leptin [ng/ml]</td>
<td>11.0 (2.44)</td>
<td>25.0 (2.7)*</td>
</tr>
</tbody>
</table>

Data extracted from Maurer L. et al., 2017

Data extracted from Sörhede M. et al., 2004
NAFLD: Non-Alcoholic Fatty Liver Disease, CVD: Cardiovascular disease, GB: Gallbladder

Image extracted from Bray G., 2004
NAFLD: Non-Alcoholic Fatty Liver Disease, CVD: Cardiovascular disease, GB: Gallbladder
**Diabetes** is a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar), which leads over time to serious damage to the heart, blood vessels, eyes, kidneys, and nerves.

*Risk factors:* age, genetic background, unhealthy diets and physical inactivity.

108 million adults (>18) had diabetes in 1980. It was 422 million by 2014.
TYPE 1 DIABETES
Body does not produce enough insulin

Symptomatology:

- Always hungry
- Unexplained weight loss
- Numb or tingling hands/feet
- Frequent urination
- Sexual disorder
- Extreme fatigue
- Always thirsty

Information extracted from the World Health Organization (WHO) and The Rotterdam Study webpage

December 01, 1999; 53 (9) ARTICLES

Diabetes mellitus and the risk of dementia
The Rotterdam Study

Alzheimer’s disease is a neurodegenerative relentless pathology, currently with a chronic and incurable prognosis.

- Related to decreases in the weight and volume of the brain. Also, there is an atrophy of the cerebral gyrus as well as dilatation of the ventricular system and hippocampus degeneration.
Alzheimer’s disease

Familial Alzheimer’s disease (5%)
- Usually appears between the age of 30-65 years of age
- Gene alteration: APP, PSEN1, PSEN2, ...

Sporadic Alzheimer’s disease (95%)
- Usually appears past the 65 years of age

Anticholinesterase drugs → Donepezil, rivastigmine, galantamine

Antagonist of glutamatergic NMDA receptors → Memantine
First diagnostic by A. Alzheimer

1907

Aluminium

1965

Cholinergic

1983 1985

Amyloid β

1992

Ionic channel

1994

Glutamatergic

1996

Mitochondrial damage

2000

Metabolic

2002

Hoyer: importance of insulin

2004

Oxidative stress

2006

Neuroinflammation

2008

Synaptic dysfunction

2010

Dendritic

2012

2014

2018

Adapted from Petrov, D., 2015.
Altered regulation of brain glucose metabolism as a cause of neurodegenerative disorders?

Blum-Degen D¹, Fröhlich L, Hoyer S, Riederer P.

Abstract

At present, search for the causes of neurodegenerative diseases represents a major topic in brain research. Acquired disturbances of cell metabolism are supposed to be a cause of the two most important neurodegenerative disorders in ageing, like senile dementia of the Alzheimer type and Parkinson's disease, resulting in measurable decreases of in vivo and post mortem cerebral glucose metabolism. Accumulating evidence indicates that insulin plays an important role in the regulation of brain glucose homeostasis in the central nervous system and has trophic effects on neurons. It has been suggested that the reduction of brain glucose metabolism in neuro-degenerative disorders may be related to a defect of the neuronal insulin-insulin receptor-interaction. It will be the aim of our study to demonstrate whether there exist any changes in the content of insulin, its receptor and/or in the functionality of the insulin receptor and its signal transduction in neurodegenerative disorders as Alzheimer's and Parkinson's disease.

Adapted from Petrov, D., 2015.
Desensitization of the neuronal insulin receptor: a new approach in the etiopathogenesis of late-onset sporadic dementia of the Alzheimer type (SDAT)?

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Received 15 December 1994; revision received 13 January 1995; accepted 30 March 1995

Brain glucose metabolism is controlled by amplification and desensitization of the neuronal insulin receptor.

Hoyer S1, Henneberg N, Knapp S, Lannert H, Martin E.

Causes and consequences of neuronal energy deficit in sporadic Alzheimer's disease.

Bauer J1, Piacsche K, Martin E, Bardenheuer HJ, Hoyer S.


Hoyer S3.

Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease

TYPE 1 DIABETES
Body does not produce enough insulin

TYPE 2 DIABETES
Body produces insulin but can’t use it well

GESTATIONAL DIABETES
A temporary condition in pregnancy

TYPE 3 DIABETES
Brain-related insulin resistance

Adapted from World Health Organization (WHO)
TYPE 3 DIABETES
Brain-related insulin resistance

Adapted from World Health Organization (WHO)
Type 3 Diabetes: Cross Talk between Differentially Regulated Proteins of Type 2 Diabetes Mellitus and Alzheimer’s Disease

Khyati Mittal*, Ruchi Jakhmola Mani* & Deepshikha Pande Katare

Type 3 Diabetes (T3D) is a neuroendocrine disorder that represents the progression of Type 2 Diabetes Mellitus (T2DM) to Alzheimer’s disease (AD). T3D contributes in the increase of the total load of Alzheimer’s patients worldwide. The protein network based strategies were used for the analysis of protein interactions and hypothesis was derived describing the possible routes of communications among proteins. The hypothesis provides the insight on the probable mechanism of the disease progression for T3D. The current study also suggests that insulin degrading enzyme (IDE) could be the major player which holds the capacity to shift T2DM to T3D by altering metabolic pathways like regulation of beta-cell development, negative regulation of PI3K/AKT pathways and amyloid beta degradation.
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**Nutrition and Obesity**

**Diabetes**

**Alzheimer’s disease**

**c-Jun N-terminal Kinases**

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**Novel object recognition**

- **WT 3M**
- **APP 3M**
- **WT 6M**
- **APP 6M**

**Discrimination Ratio**

- **WT 3M**
- **APP 3M**
- **WT 6M**
- **APP 6M**

**Mouse Aβ42 soluble**

**β-amyloid / mg protein**

- **WT 3M**
- **APP 3M**
- **WT 6M**
- **APP 6M**

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Extracted from Ettcheto M. et al., 2016

Extracted from Pedrós I. et al., 2016
Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease – is this type 3 diabetes?

Article type: Research Article
Authors: Steen, Eric | Terry, Benjamin M. | J. Rivera, Enrique | Cannon, Jennifer L. | Neely, Thomas R. | Tavares, Rose | Xu, X. Julia | Wands, Jack R. | de la Monte, Suzanne M.

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Alzheimer's Disease Is Type 3 Diabetes—Evidence Reviewed

Suzanne M. de la Monte, M.D., M.P.H.1-3 and Jack R. Wands, M.D.3

Brain Insulin Resistance and Deficiency as Therapeutic Targets in Alzheimer's Disease

Suzanne M. de la Monte*
**Is the actual approach to treating Alzheimer’s disease right?**

Are antidiabetic drugs or Insulin Receptor modulators actually the key to controlling the disease?

Studies carried out by the research team at Warren Alpert Medical School at Brown University identified the possibility of a new form of diabetes after finding that insulin resistance can occur in the brain.

Lead researcher, Dr Suzanne de la Monte, carried out a further study in 2012 to further investigate the link.

The researchers pinpoint resistance to insulin and insulin-like growth factor as being a key part of the progression of Alzheimer’s disease. [61]

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**Brain Insulin Resistance and Deficiency as Therapeutic Targets in Alzheimer's Disease**

Suzanne M. de la Monte*
**Nutrition and Obesity**

**Diabetes**

**Alzheimer’s disease**

**c-Jun N-terminal Kinases**

- **Inhibitors of the Insulin Receptor Substrates**
- **Part of the Mitogen-Activated Protein Kinase family**
- **Codified by Mapk8, Mapk9, Mapk10**
- **Response elements to stress stimuli (cytokines, UV, heat shock, osmotic shock,...)**
- **Isoform differential body distribution**

**Diagram:**
- Insulin
- Insulin Receptor
- Insulin Receptor Substrate
- Phosphoinositide 3-kinase
- Protein Kinase B
- Glut4
- Glucose uptake
- MEKK1 MEKK4 MEKK2 TAK1 ASK1 MLK3 MEKK3 MEKK6
- MEK1/2 MEK1/2 ERK1/2 Elk-1 c-Myc
- Migration MMPs, cytokines, VEGF, apoptosis
- p38α/β/γ/δ ATF2, Elk-1, MAPKAPK2
- JNK1/2/3
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