

# Alzheimer's Disease and Trace Elements: Chromium and Zinc

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## Introduction

The most frequently occurring form of senile dementia is Alzheimer's Disease (AD). The progression of the disease leads to a loss of cognitive abilities. For this reason, the treatment of AD. Is a great challenge for modern medicine. Its cause is unknown.

The illness has two distinct forms: early-onset and late-onset AD. Late-onset AD is also referred to as the sporadic form (90–95%) This form occurs much more frequently than early-onset AD (= genetic form) (5–10%). It is as yet unclear whether the amyloid plaques and neurofibrillary tangles are the causes of AD or simply the result of other pathological Processes.

A multitude of patho-anatomical, biochemical and neurophysiological study results have lead to the discussion of a number of different hypotheses regarding the pathogenesis of AD.

## The Cholinergic Hypothesis

The cholinergic hypothesis assumes that the cognitive deficits associated with AD can be attributed to the reduced function of the cholinergic neurotransmitter system. Indications for this hypothesis are the loss of cholinergic neurons in Alzheimer's patients and a correlation between cholinergic deficits and cognitive disorders. Improvement of symptoms in Alzheimer's patients is seen given treatment with ACh-E inhibitors. The therapy principle of choline esterase inhibition has one disadvantage. It is dependent on the pre-synaptic cholinergic activity still present.

## Disorders in the Glutamatergic System: a Further Hypothesis

In addition to disorders of the cholinergic system, disorders in the glutamatergic system play an important role in the origin of dementia. Glutamate is an important excitatory neurotransmitter in the CNS. Seventy percent of all excitatory neurons have glutamatergic neuro-transmission, Physiological glutamatergic neurotransmission is the basis for a normal synaptic transmission.

In patients with dementia, a considerable loss of glutamate receptors in the cortex and hippocampus has been observed. With pathological conditions, an increase in glutamate in the synaptic gap has been detected. The increase in the glutamate concentration causes the activation of the catabolic enzymes and neuron death. A NMDA receptor antagonist can block the NMDA receptor in the presence of slightly raised concentrations of glutamate and improve the synaptic activity. In this manner, the dementia symptoms are reduced.

## Hypothesis of a Cascade-like Process of Disturbances in the Neuronal Glucose and Energy Metabolism

Researchers assume that heterogeneous factors are involved in the development of the sporadic form of Alzheimer's. The sporadic form of Alzheimer's can be described as a metabolic illness of the brain.<sup>1</sup> Of importance here are:

- a) The age of the person with the biological consequences on the brain tissue;
- b) A disruption of the neuronal insulin signal transduction. This is the cause of the acetylcholine and energy shortages which leads to an imbalance in the activities of the cellular phosphates and kinases.
- c) A membrane instability.  
A disruption of neuronal insulin receptor

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signal transduction is an early and central pathophysiological occurrence with Alzheimer's. Here we seem to be dealing with a metabolic disorder, in the form of diabetes mellitus type 2, that affects the brain metabolism.<sup>1</sup>

#### Brain Metabolism and Hyperglycosemia

Type 2 diabetes is typical in persons of advanced age. Insulin resistance is the cause of type 2 diabetes. There is a close connection between glucose and insulin metabolism and brain metabolism.

Diabetes mellitus can be connected to the development of a dementia syndrome. Hyperglycemia leads to the increased production of glycolization and advanced glycolization end products (AGE) which can contribute to the beta-amyloid plaques associated with AD.

Glucose metabolism is of central importance for the brain and for neurons. The healthy brain uses glucose exclusively to create energy in the form of ATP. With ATP deficiencies, all ATP-dependent processes are reduced. The regulation of the neuronal glucose metabolism is changed at advanced ages by the reduction of insulin signal transduction. Insulin concentrations in the brain, the number of insulin receptors and the activity of the tyrosine kinases diminish with increasing age. An association between diabetes mellitus type 2 and Alzheimer's disease is the result of two extensive cross-section studies of aged populations.<sup>2,3</sup> The neuronal glucose metabolism is regulated by the neuronal insulin signal transduction system. Disruptions lead to abnormalities in glucose and energy metabolism similar to those found with diabetes mellitus type 2.

#### Chromium Disruption of Glucose Tolerance

Trivalent chromium is an essential element for normal carbohydrate metabolism and normal insulin sensitivity. Wada and Yamamoto have isolated a chromium-binding oligopeptide. It is referred to as low-molecular-weight-chromium-binding-substance (LMWCr) of chromodulin.<sup>4</sup> The name

chromodulin was chosen as an analog to the calcium-binding protein calmodulin. Chromium is excreted following the addition of insulin in the form of the oligopeptide chromodulin. No other naturally occurring chromium compound amplifies the metabolic effect of insulin in a comparable manner.<sup>5</sup>

Studies with the oligopeptide on adipocytes in rats showed two effects:

1. Lowered activation of the membrane protein tyrosine phosphatases.
2. Significant insulin-dependent stimulation of the insulin receptor tyrosine kinase activity.

In the presence of insulin, chromodulin causes eight times the stimulation of the protein tyrosine kinase activity. This stimulation cannot take place without insulin.<sup>6</sup> Using cell cultures of the liver cells of rats, it was shown that chromium present in body cells as an oligopeptide complex, is essential for the effectiveness of insulin and thus for glucose metabolism.<sup>7</sup> Chromium ions increase insulin-stimulated tyrosine phosphorylation and thereby modulation of cellular insulin signaling.

#### Zinc and Brain Metabolism

For a number of years now, the essential importance of zinc for brain metabolism has been the focus of research. Burnet described the hypothesis of a zinc deficit as the cause of dementia.<sup>8</sup> Zinc deficits have been demonstrated in the hippocampus and in the cerebral cortex.

The protein tyrosine kinase is significantly reduced in the hippocampus with AD, but can be activated with the addition of zinc.

Intracellular zinc can be regulated through MT (metallothionein) or MT isoenzymes. High concentrations of metallo-thionein-III are present in the hippocampus and cerebral cortex. Neurons have mechanisms for zinc absorption. Zinc is present in synaptic vesicles. One also refers to a zinc-containing neuron, which are grouped with the glutamatergic

neurons. The involvement of zinc in glutamatergic functions is possible in three areas: the synaptic vesicle, the synaptic gap and the post-synaptic membrane.

Zinc has an important neuromodulating function in glutamatergic synapses. Micromolecular zinc concentrations can inhibit N-Methyl-D-Aspartate (NMDA) receptors. It is assumed that the expression of MT isoenzymes can be correlated with the stage of AD and the cellular zinc status.

Studies of adipocytes show an insulin-like effect under zinc incubation. Zinc has a stimulatory effect on lipogenesis *in vitro* that is comparable to the effect of insulin. The administration of both components has an additive effect.<sup>9</sup>

As measurements of the effectiveness of zinc on glucose absorption in the presence of insulin or zinc in cell cultures have shown, zinc exhibited an increase in the Phosphorylation with both tyrosine residues and serine residues. Insulin, like zinc, increases the tyrosine phosphorylation of insulin receptor beta sub-unit. A zinc deficiency can impair the optimal functioning of insulin signal transduction.<sup>10</sup> The insulin-saving effect of zinc has been proven with diabetes mellitus type 1.<sup>11</sup> Long-term studies confirm these results.<sup>12</sup> Zinc in the urine is found with both diabetes mellitus type 1 and diabetes mellitus type 2.

## Discussion and Conclusion

The hypothesis of a cascade-like process for the pathogenesis of AD, poses the central question is: is the sporadic form of AD the result of metabolic disturbances in the brain? This would be supported by the fact that a glucose and energy deficit in the brain could represent the beginning of a cascade-like process. The main causes are assumed to be:

a) Age in connection with the Presence of susceptibility genes with the addition of adult lifestyle risk factors, which set the pathophysiology specific to sporadic AD in motion.

b) A disturbance in neuronal insulin signal transduction.

c) A membrane instability, of which oxidative stress is one of the causes.

There are very few reports regarding treatment results with Alzheimer's patients given zinc supplements. Constantinidis reports positive treatment results with Alzheimer's patients.<sup>13</sup> One pilot study describes a dramatic improvement for three of six patients with zinc supplementation.<sup>14</sup>

During zinc therapy for *acrodermatitis enteropathica*, an inherited zinc deficiency syndrome, one regularly sees a positive effect on the psyche of the patients, including improvement in mood, thinking ability, productivity and enjoyment of life. Chromium in the form of chromium picolinate can be used adjuvantly with depressive disorders. An improvement in mood and performance have been unanimously reported. In casuistics, diabetics are often mentioned. The working mechanism is under discussion. Psychiatrists report a quick, at times described as dramatic, improvement of psychiatric symptoms within a few days when using chromium as an additional medication in the treatment of dysthymic disorders with a tricyclic antidepressant. It induced a lightening of mood and increase in energy. Some patients described a caffeine-like effect.<sup>15</sup>

With the pathogenesis of AD, a reduction of the neuronal glucose and energy metabolism is assumed. At the center of this lies a disruption of the insulin signal transfer. Current results of biochemical studies indicate that chromium and zinc are of importance to brain insulin signal transduction system.

With the therapeutic use of chromium and zinc, the fact that exogenic and endogenic factors must be taken into consideration for the bio-availability of these and other trace elements is often overlooked. These factors include a special diet, which is indispensable for diabetes mellitus type 1.

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