Seong-Wook Yun
Dr. sc. hum.

Effects of low-level lead treatment on behavior, cognition and cerebral energy metabolism in adult and aged rats

Geboren am 25. 12. 1968 in Seoul/Korea
Reifeprüfung am Dez. 1986 in Chunchon/Korea
Studiengang der Fachrichtung Gen Technologie vom SS 1987 bis WS 1990/1991, Vordiplom am 20. 02. 1991, und Virologie vom SS 1991 bis SS 1994, Diplom am 20. 08. 1994 an der Hallym Universität/Korea

Promotionsfach: Pathologie
Doktorvater: Prof. Dr. med. S. Hoyer

The present study was designed to investigate the effects of a widely distributed toxic substance, Pb on behavior, cognition and brain energy metabolism, particularly in the aging stage and in the pathophysiological condition of energy shortage.
In experiment 1, middle-aged rats (15 months old) were exposed to 200 ppm Pb acetate in drinking water for 2 months and thereafter received bilateral intracerebroventricular injections of streptozotocin (STZ). After 1 month's additional exposure to the same level of Pb solution as before the rats were sacrificed either in steady state for biochemical analysis or perfused for immunohistochemical examination. Blood and brain Pb levels were measured by graphite furnace atomic absorption spectrophotometry. Energy-rich phosphate levels in the brain were determined by HPLC equipped with a UV detector. Astroglial activation and glucose-regulated protein (GRP)94 expression were examined immunohistochemically. Exposure to Pb increased the blood Pb level to 10.8 μg/dl and the brain Pb level to 0.052 μg/g. A significant additional increase in the brain Pb level, to 0.101 μg/g, became obvious in rats treated with Pb+STZ. Both Pb and STZ induced perturbation in brain energy metabolism, but no further alteration in energy metabolite levels was found in rats treated with Pb+STZ. Astroglial activation and GRP94-positive astrocytes and neurons were found only in the brains of Pb+STZ-treated rats.
In experiment 2, the effects of 3-month-Pb treatment on behavior and brain metabolism were investigated with middle aged rats (12-month old). In this experiment it was not possible to find any behavioral and cognitive abnormalities, furthermore, the energy-rich phosphate levels in the parietotemporal cortex of the Pb-teated rat brains were same as those of controls.

In experiment 3, adult (10-month-old) Wistar male rats had been exposed to 200 ppm Pb acetate in drinking water for 12.5 months. After 12.5 months' exposure the mean Pb levels in blood and brain had increased to 17.5 μg/dl and 0.07 μg/g, respectively, and the rats showed obviously impaired learning and memory function in a holeboard spatial memory test. However, in a locomotor activity test and a passive avoidance test no significant difference was found between experimental and control groups. Mild abnormalities in energy-rich phosphate concentrations were found in the parietotemporal cortex and hippocampus but only the 4.4% decrease of ATP in the parietotemporal cortex was statistically significant.

In experiment 4, the inhibitory effects of low-level lead on brain hexokinase, glyceraldehyde-3-phosphate dehydrogenase, pyruvate kinase and pyruvate dehydrogenase complex with rat brain homogenate. Pyruvate dehydrogenase was distinctively inhibited when low-dose lead acetate was added last of all (IC_{50}=5 μM) to the reaction mixture. The other enzymes were completely resistant to 5 μM of lead acetate. When the homogenate was preincubated with Pb acetate hexokinase was dramatically inhibited by low-level of Pb acetate (1-5 μM), in a manner dependent on both preincubation time and lead concentration. However, the inhibitory effect was abolished by coincubation with its substrates, glucose or ATP.

The results of the present study suggest that low-level Pb can be a potential risk factor or metabolic accelerator in the cognition impairment and some neurodegenerative disorders frequently developing during the aging period such as senile dementia of Alzheimer type, and the impairment of glucose/energy metabolism by Pb may be regarded as an important neurotoxic mechanism.