7 Summary

Element analytical investigations revealed differences in the selenium concentrations in the tissues of the rats. Here the brain had two distinct features: it had relatively low selenium content and, with insufficient selenium intake, the brain was preferentially supplied with the element.

The results of several studies indicate that the trace element selenium in the form of selenoproteins is of essential significance for physiological processes in the CNS. It acts as a scavenger of radicals and is a component of the redox system. The sites of action and the functions of selenium in the brain are, however, not yet completely known.

The aim of this work was therefore the investigation of the distribution of selenium and of the selenoprotein expression on a regional and cellular level. The results obtained for the distribution of selenium within the rat brain by means of neutron activation analysis showed only slight regional differences. The highest selenium content in the cerebellum differed from the lowest in the brain stem by a factor of 1.6. With insufficient selenium supply the selenium content in all regions of the brain was reduced by only 30 %, but in the kidney and liver by one and two orders of magnitude, respectively. The analysis of the tissue cytosols from the different brain regions, liver and kidney by means of atomic absorption spectrometry revealed that the non–cytosolic selenium in the brain was reduced to a larger degree than the cytosolic selenium. The comparison with published data suggests that the low content of cytosolic glutathione peroxidases in the brain may be responsible for this effect.

Time course experiments on the uptake of ^{75}Se revealed a delay in the incorporation of the element into the brain compared to the liver, kidney and spleen. After metabolic labeling of rats with ^{75}Se and protein separation by SDS-PAGE and 2–dimensional electrophoresis similar distribution patterns of the ^{75}Se–containing proteins were found in all regions except in the cerebellum. A more strongly labeled 15 kDa protein spot with an IP of $4.8 - 5.2$ was observed in the cytosol of the cerebellum.

The expression patterns of the selenoproteins in the different cell types of the brain were investigated by labeling cultures of immortalized neurons, astrocytes, oligodendrocytes, microglia and cerebral endothelial cells with ^{75}Se and analysis by SDS-PAGE and 2-dimensional electrophoresis. The pattern of the selenoproteins exhibited characteristics in the case of investigated microglia and cerebral endothelial cells. An increased expression of selenium-containing proteins with molecular masses of 12.6, 10 and 9 kDa was found in the microglia. In the endothelial cells two additional 15 kDa protein spots with IP-values of $5.2 - 5.6$ and $5.8 - 6.2$ could be distinguished after 2-dimensional electrophoresis. These two endothelial cell-specific spots were also detected in the tissue of rat brain.

The molecular masses and IP-values from the published sequences of 25 human genes of selenoproteins were compared with the corresponding values of the ^{75}Se–labeled protein spots detected in the samples of the brain tissues and cell types. In this way nearly all of these selenoproteins could be assigned to the labeled proteins.

In this work a model of the blood-brain barrier was established consisting of primary astrocytes and a cell line of cerebral endothelial cells rBCEC4. In the investigation of the expression patterns of the ^{75}Se–containing proteins it was found that the expression rate of a cytosolic 15 kDa protein was strongly increased in endothelial cells which were grown in the co–culture. The same effect was observed when the culture of endothelial cells was grown after adding of the conditioned medium of astrocytes. This finding suggests the presence of soluble factors which induce the up-regulation of a specific selenium-containing protein in the blood-brain barrier.

The results of the investigations carried out in this work showed that the selenium distribution and the regulation of the selenium uptake in the different regions of the brain were very similar. The same was true for the selenoprotein expression patterns in the regions and cell types of the brain. But for some selenoproteins, however, differences in their distribution were observed which provide evidences on specific sites of action and specific functions of these compounds.