Anhang: Summary

The transmembrane domains of integral membrane proteins show an astounding accumulation of tyrosine and tryptophan residues, especially in the membrane region with the highest lipid density. It is shown that these residues perform vital antioxidant functions inside lipid bilayers and protect cells from oxidative destruction. First, tyrosine- and tryptophan-containing peptides representing stretches from the transmembrane domains of different integral membrane proteins prevent oxidative lysis in neuronal cells. Second, long-chain acylated tyrosine and tryptophan, but not phenylalanine, other amino acids, or short-chain acylated derivatives, are potent inhibitors of intracellular peroxide accumulation, lipid peroxidation, and oxidative cell death of clonal cells, primary neurons and organotypic slice cultures. The antioxidant functions of tyrosine and tryptophan provide a specific explanation for (*i*) their unique transmembrane distribution pattern and (*ii*) the high vulnerabiliy of low-protein neuronal membranes to oxidative stress, which is a characteristic phenomenon observed in neurodegenerative disorders. Due to their high antioxidant efficacy and their presumed active passage through the blood-brain barrier, long-chain acylated tyrosine and tryptophan derivatives might be very promising lead structures for neuroprotective drug design.

A second novel class of endogenous antioxidant structures whose radical-modulatory effects are based on tyrosine and tryptophan residues, are peptide hormones. The short-chain secretory peptides luteinizing hormone releasing hormone (LHRH), enkephalin, angiotensin, and oxytocin, are biochemical antioxidants in aqueous medium. They directly scavenge free peroxyl radicals, they prevent the oxidation of low-density lipoprotein, and they inhibit lipid peroxidation in brain membranes. Their capacity to directly suppress free radical-mediated reactions is demonstrated by electron spin resonance spectroscopy. Electrospray ionisation mass spectrometry analysis of the free radical-quenching reaction reveals distinct oxidation products, including peptide dimers. Moreover, secretory peptide hormones can scavenge reactive nitrogen species derived from nitric oxide and peroxynitrite. A structure-activity relationship analysis indicates that their antioxidant activity is based on the occurrence of solvent-exposed tyrosine and tryptophan residues, which is consistent with the mass spectrometry results. Significant effects in vitro can be observed at nanomolar concentrations, which makes these peptides comparable in potency to classical low molecular mass antioxidants. It is concluded that (*i*) secretory peptide hormones may constitute an important part of the endogenous antioxidant defence system, and that (*ii*) the immediate chemical interaction between radical signalling molecules and peptide hormones might represent a

special type of direct cross-talk between biological signals. The potential of the described novel antioxidant molecules with respect to drug design and pharmacological use in human disease is discussed.

Finally, the elucidated general antioxidant properties of tyrosine- and tryptophan-based cellular structures are combined with biochemical knowledge from other disciplines leading to the hypothesis that tyrosine and tryptophan may be two young amino acids from an evolutionary point of view, whose advent might have been triggered by the appearance of molecular oxygen in the biosphere 2.5 billion years ago.