CAN ANTI-INFLAMMATORY DRUGS BENEFIT NEURODEGENERATIVE DISEASES?

A. Ludolph
University of Ulm, Germany
albert.ludolph@rku.de

There is no doubt that neuroinflammation is present in human neurodegenerative diseases and models of these diseases.
However, it is doubtful that this observation means anything for therapy in humans. Why is this so?

1. Animal models do not precisely reflect the human diseases. This is underlined by our own experiences in the ALS models: whereas copaxone had a large effect in the low-copy strains of the Cu/Zn SOD transgenic mice, we did see only a minor effect in the high copy animals, if any.
2. Therapeutic effects are based on experiences in chronic inflammatory diseases of the nervous system, such as multiple sclerosis. It remains unproven that inflammation in these diseases resembles the one seen in neurodegenerative diseases, such as Alzheimer´s, Parkinson's disease or ALS. For example, studies in chimeric animals show in ALS models, that in sharp contrast to multiple sclerosis, inflammation seems to contribute to the progression of the disease, but not to its initiation. Also, levels of inflammatory markers are increased in the CSF of ALS patients, but not to a degree as seen in typical inflammatory diseases of the nervous system.
3. It is unknown whether this seemingly low-level inflammation is harmful to nerve cells. It remains unproven whether inflammation remains innocent during the disease process. It may be even beneficial or protective to the malfunctioning or dying neuron.
4. The word neuroinflammation by itself does not mean anything in toxicological terms. The potentially harmful or beneficial effect of inflammation is like each neurotoxic process dose-dependent. The dose-effect curve might also be dependent from target cells; a given dose might be protective for one cell population whereas it might be harmful for the other. There might be differences of dose-response curves for neurons, astrocytes and endothelial cells.
5. Practical experience tells that these arguments are of relevance given the negative experience with large personal and financial investments into human neuroprotection with minocyclin, copaxone and recently pioglitazone. Early experience with uncontrolled exposure of patients with neurodegenerative diseases to radiation and immunosuppressants are consistent with the results of these controlled observations.

I conclude that recent experience tells that much needs to be known before the principles of modulation of inflammatory cells of the nervous system – like done in multiple sclerosis – can successfully be transferred to neurodegenerative diseases such as Alzheimer´s, Parkinson´s and ALS.

o