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# *Chapter V*

## On excitotoxicity

### *Introduction*

The papers in the following chapter are all focussed on a general theme of excitotoxicity. The work described in each of the contributions, however, is representative of different trends in the spectrum of excitotoxicity research, and thus provides a broad-based, albeit necessarily incomplete, perspective on the field.

In 1991 Dr. Cosi and her collaborators were the first group to hypothesize a role for poly(ADP-ribose) polymerase (PARP) in excitotoxicity, and this enzyme has subsequently become one of the great points of interest in this field. Over the last 8 years Cosi and her group have demonstrated the role of PARP in modulating brain energy metabolism in response to free radical-induced DNA damage. This has obvious implications for both excitotoxicity and neurodegeneration. The paper presented herein reviews some of this previous work and describes new findings about the involvement of PARP, and the neuroprotective properties of PARP inhibitors, in both "in vitro" and "in vivo" models of neurodegeneration. The authors make the case that their models are pertient to both acute and progressive neurodegenerative disorders such as stroke and disease, and suggest that PARP is a novel target for the development of new drugs that will be effective in the treatment of neurodegenerative disorders.

The paper by Dr. J.-C. Martel, in collaboration with Dr. M. Marien, describes part of a larger and novel research effort aimed at studying the hypothesis that the locus-coeruleus/noradrenergic (LC-NA) system controls mechanisms of cellular repair and compensation in response to brain injury. By extrapolation, deficits or dysfunction in the LC-NA may be a critical factor in the progression of a family of central neurodegenerative diseases including, but not restricted to, Parkinson's, Alzheimer's and Huntington's disease. In the present contribution the authors present data on the neuroprotective properties of alpha-2 adrenoceptor antagonists in an in vivo model of excitotoxicity that uses quinolinic acid to produce a selective lesion in the rat striatum.

The paper by Dr. Uberti, Dr. Grilli and Dr. Memo deals with the emerging consensus that the activation of specific glutamate receptor subtypes may lead to the expression of genes whose products trigger intracellular events controlling neuronal cell death. This group was the first to suggest that excitotoxicity may be associated with the activity of the transcription factor

NF-kB. They have proposed that NF-kB proteins are among the initial orchestrators of the glutamate-induced apoptotic program. Also involved is transcription factor p53, which is located downstream form NF-kB activation, but at the present time the p53 target genes triggered by glutamate receptor stimulation are largely unknown. Dr. Memo's group hypothesizes that up-regulation of the p21 and MSH2 genes, in the experimental paradigm of glutamate-induced neuronal death, is one of the consequences of the increased transcriptional activity of p53. On these bases they propose that NF-kB, p53, p21 and MSH2 maybe relevant contributors to glutamate-induced apoptosis, and the fact that these proteins are also involved in cell cycle regulation supports the proposal that aberrant expression of mitotic proteins is involved in programmed neuronal cell death.

Finally, the paper by Díaz-Trelles and colleagues describes the novel finding that terfenadine, a common antihistaminergic drug, protects neurons from the excitotoxicity produced by activation of voltage sensitive sodium channels. These authors provide evidence that terfenadine acts as a blocker of voltage sensitive sodium channels at nanomolar concentrations; an effect that is independent of any action at histamine receptors. These exciting findings open up new possibilities for the use of terfenadine or related drugs in both experimental investigations of excitotoxicity and prevention and treatment of acute and chronic disorders involving excitatory amino acid neurotransmission.

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