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Amino Acids

General Introduction: Neurobiology at the 8th International Congress on Amino Acids and Proteins, Rome, Italy, September 2003

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Rome, Italy, was the place for the 8th International Congress on Amino Acids and Proteins, organised and chaired by Professor Simone Beninati, Tor Vergata University of Rome, and hosted by Professor Enzo Agostinelli, University La Sapienza, Rome, Italy. The meeting attracted a number of neurobiologists from Europe, Asia and America, who shared their experiences and participated at invited lectures, symposia and poster sessions. The papers and symposia presented at the Neurobiology Session dealt with several issues related to neurodegeneration, focusing on metabolic insults, stress, signalling, neuroprotection and drug resistance. As for previous Congresses on Amino Acids and Proteins, the participants to the Neurobiology Session were invited to submit a paper summarising or complementing their presentation.

Thus, this Special Issue of amino Acids comprises several chapters, containing reviews and original papers, organised, and edited by the corresponding chairmen, who have further introduced the subjects, setting a framework for the contributions.

Neurodegeneration has been a general topic of this Special Issue, which has gained relevance in an increasingly aging population world-wide, where neurodegeneration and neurodegenerative diseases are permanent menaces to genetically vulnerable, but also to individuals exposed to identified or non-identified pollutants. Neurodegeneration implies severe consequences for the suffering individuals, as well as for society. The common hallmarks of neurodegenerative diseases are (i) neuronal loss, (ii) neurite atrophy and/or (iii) molecular abnormalities, whenever they are caused by genetic, developmental, metabolic and/or environmental factors. Neuronal loss is probably the final stage, preceded by neurite atrophy and other synaptic mismatches. It is not know yet whether the molecular abnormalities observed in several neurodegenerative diseases are causes, or consequences of neurotoxic conditions, or whether they represent attempts to compensate or interrupt deleterious conditions, elicited by adverse genetic or environmental conditions (Palomo et al., 2004).

While genetic susceptibility is the main factor for some low frequency neurodegenerative diseases, such as trinucleotide repeat disorders, Huntington's disease, Cu/Zn superoxide dismutase-1-related amyotrophic lateral sclerosis, environmental and developmental factors are prominent in the majority of the cases. Aging is perhaps the greatest risk factor in sporadic forms of neurodegenerative diseases, although it is not clear if that risk refers to clinical signs rather than to cell loss properly. Although cell loss can occur from early developmental stages, aging probably implies a cumulative cell loss over time. Hence, the hallmark is perhaps a decreased capacity for cellular regeneration, and/or a decreased viability of cell cycle checkpoint defenses. A main feature of major neurodegenerative disorders, such as Alzheimer's (AD) and Parkinson's (PD) diseases, is however their progressive and often insidious development, determining that the clinical onset of the disease is first discovered when important cell loss has already occurred.

The concept of long-term effects produced by metabolic insults occurring along development has been explored by papers of the first chapter, whether these metabolic insults occur during pregnancy (León Navarro et al., 2005), or at perinatal (Klawitter et al., 2005) and/or neonatal (Kusama-Eguchi et al., 2005) stages. The involvement of excitatory amino acids is investigated, identifying exogenous and endogenous ligands eliciting excitotoxic cascades and oxidative stress. The effects are rather plastic, because of system compartmentalization, and because of post-transcriptional modulation, leading to down- or

up-regulation of different proteins, preventing, or perhaps, further increasing cellular impairment. Cellular impairment can then be expressed as cellular loss, or neuritogenesis and/or neurocircuitry atrophy. Pharmacological treatments can, under those conditions, substitute for missing messengers, as for the case of L-DOPA, but that treatment can also stimulate neurotrophic mechanisms, promoting or priming the expression of neurotransmitter receptors (Kostrzewa et al., 2003, 2004, 2005). While not primarily aimed to a particular neurotransmitter, some drugs, including those used for anaesthesia, produce long-term effects that can only be explained by actions on particular neurocircuitries. These actions have to be investigated in order to explain unexpected side effects, such as hallucinations, sexual disinhibition or euphoria produced by drugs like propofol. Thus, Grasshoff et al. (2005) report here about the modulation of dopamine and glutamate release by intravenous propofol.

The second chapter focuses on glutamatergic signalling, describing sequence variation among the genes encoding for ionotropic glutamate receptors (Lipsky et al., 2005), and exploring on the dynamics of intracellular calcium signalling following activation of NMDA receptor and voltage sensitive calcium channels (Cupello et al., 2005). The enlightening of the properties of glutamate receptors in relation to cell function provides pharmacological opportunities, leading to drugs like nefopan, that can prevent NMDA-mediated excitotoxicity (Novelli et al., 2005). Papers by Tasker et al. (Doucette et al., 2004; Tasker et al., 2005) investigates on the interplay between NMDA and non-NMDA receptors, suggesting that kainate receptors may play a role in psychiatric disorders, such as schizophrenia.

Oxidative stress plays a crucial role as a cause or a complication of several diseases, associated or not to metabolic and/or ischemic/hypoxic insults, affecting individual organs or the full organism. Glaucoma is a neurodegenerative disease associated to vascular dysregulation and local ischemia/reperfusion, which has been a main subject of the third chapter of this Special Issue. Yeghiazaryan et al. (2005) investigated the role of ABC1 transporter in vascular regulation, showing that its expression rate is increased in leukocytes of glaucoma patients, suggesting a systemic anormality. That increase may have therapeutic relevance, since ABC1 acts as an energy-dependent unidirectional trans-membrane cholesterol efflux pump that can export a wide range of hydrophobic drugs (see Trog et al., 2005). A decreased expression of XPGC, a gene related to DNA-repair, has been found in circulating leukocytes of normal-tension glaucoma patients. Moenkemann et al. (2005) have further investigated this issue, finding that the anti-apoptotic factors, $P21^{WAF1/CIP1}$ and 14-3-3σ, are elevated in normal- and high-tension glaucoma patients, but the factor $P21^{WAF1/CIP1}$ is higher in high-tension glaucoma patients, suggesting that up-regulation of $P21^{WAF1/CIP1}$ in circulating leukocytes of vasospastic individuals may indicate an increased risk for developing glaucoma.

Oxidative stress also plays a role in the development of diabetic complications. Thus, Kapalla et al. (2005) showed that several stress responsive genes are over expressed in leukocytes of diabetic patients compared to non-diabetic individuals, suggesting that differential expression might represent a potential risk factor for diabetic complications. Furthermore, the deposition of advanced glycation end products is enhanced in diabetes mellitus, being linked to complications such as microvascular diseases. Glycated proteins have receptors on mononuclear blood cells, generating reactive oxygen species that can modify gene expression. Hence, Golubnitschaja et al. (2005) show evidence suggesting that there is a functional link between specific alterations of gene expression in mononuclear blood cells (i.e. recoverin, MMP-2 and MMP-9), increase of serum matrix proteases activity and the extent of proliferative retinopathy in diabetes mellitus patients.

The Satellite on Neurobiology at the International Congresses of Amino Acids and Proteins is established as a forum for discussing the role of amino acids, calcium homeostasis, metabolic and ischemic/hypoxic insults, oxidative stress, gene expression, neurotoxicity and neurodegeneration. The Editors are now preparing to organise a Satellite on Neurobiology at the 9th International Congress on Amino Acids and Proteins, including brainproteins, that is back to Vienna, Austria, August 8–12, 2005.

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