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Special Issue: Amino Acids in Neurobiology

Amino acids in neurobiology: Neuroprotective and neurotoxic aspects of amino acids involved in neurotransmission and neuromodulation – General Introduction

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The *7th International Congress on Amino Acids and Proteins* (August 6–10th, 2001) went back to Vienna, Austria, to be chaired again by Professor G. Lubec (Dept. of Paediatrics, Vienna University, Vienna, Austria) and, as in previous occasions, the meeting was a forum for discussing about the role of amino acids in the CNS.

The meeting took place in the framework provided by the publication of the working drafts of the human genome by the International Human Genome Sequencing Consortium, led by F. Collins (2001) and Venter et al. (2001), on February 15th, and 16th, 2001, respectively.

The finding that only 26,000 to 38,000 genes are found in the draft versions of the human genome is especially challenging for neuroscientists, since a human brain contains some 10^{11} neurons and even more glial cells, implying that not genes (or nucleic acids), but proteins and amino acids are the "*executive molecules*" of life. Thus, we have to look beyond genomes to proteomes to demystify the functions of the proteins coded by the genes.

All possible proteins participating in cellular function are encoded in the genome sequences, but a single gene can encode multiple different proteins, by (i) alternative splicing of the mRNA transcript, (ii) varying translation start or stop sites, or (iii) frameshifting, translating a different set of triplet codons. Proteins undergo important changes after being built from their gene templates, being modified by processes like phosphorylation, glycosylation, acetylation, ubiquination, farnesylation, and adapt further by changing their location within the cell, being cleft into active and/or inactive fragments, adjusting their stability, or changing what they bind to. A single protein may then be involved in more than one process, and similar functions may be carried out by different proteins, or by their products, peptides and amino acids. These three components are essential for metabolic pathways, required for the development and function of the central nervous system (CNS), precursors for the synthesis of several neurotransmitters, and neurotransmitters themselves. Furthermore, drug targets are almost always proteins.

Protein dysfunctions are associated to several diseases. So called "proteopathies" can be found, by example, in Alzheimer's disease, where aggregation of β-amyloid together with plaque associated proteins, functioning as pathological chaperones, are prominent. In Huntington's disease there is genetic defect, resulting in CAG triplets yielding polyglutamine containing proteins. In both cases, protein faulty expression and/or malfunctioning lead to cell death and the characteristic symptoms.

Thus, in the wonderland of complete sequences, the future still belongs to proteomics, identifying and quantifying proteins and their products, and ultimately determining their function, and identifying pathological conditions in which proteins are involved.

Glutamate and γ-aminobutyric acid (GABA) represent the major neurotransmission systems in the brain. Glutamate has long been discussed as an exclusively excitatory transmitter. However, inhibitory functions via adenylate cyclase coupled metabotropic receptors have recently been described. Thus glutamate needs now to be considered as an excitatory, as well as in-

hibitory transmitter. GABA is still only an inhibitory signal, producing hyperporalisation, upon binding to GABAergic receptors. Glutamate and GABA are responsible of the main work, while the other systems could be considered as followers or modulators of the work performed by the main neurotransmitters.

Glutamate is ubiquitously distributed, apart of its stimulatory functions it induces toxicity when the overflow of glutamate is increased following metabolic disturbances, or when glutamate receptors are overstimulated by endogenous or exogenous substances. Glutamate is also a precursor of several metabolic steps, included that for the synthesis of GABA. Overflow of glutamate together with its action is regulated by a potent transport carrier system, to neurons and astrocytes, and a complex and sophisticated set of receptors, whose number and functions are still largely unexplored.

As shown in Fig. 1, several glutamate receptor types have been described and already cloned and sequenced, representing two large families, ionotropic and metabotropic receptors. Among the ionotropic receptors, several subgroups have been identified, encoded by at least six gene families, as defined by sequence homology, scattered over numerous chromosomes (see Dingledine et al., 1999). (i) N-methyl-D-aspartate (NMDA) R1 (NR1) and NMDAR2A-2D (NR2A-D), belonging to the NMDA receptor subtype (comprising three gene families); (ii) the GluR1-GluR4 to the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor subtype (a single gene family), and (iii) the GluR5-7, KA1 and KA2 to the kainate (KA) receptor subtype (two gene families).

The metabotropic receptors (mGluR) have been sub-classified according to pharmacological affinities, similarities of primary sequences, and/or second messenger systems (Houamed et al., 1991; Tanabe et al., 1992). Thus, (i) the mGluR1 and mGluR5 subtypes are most potently stimulated by quisqualate, have extensive sequence homology, and increase phosphatidylinositol turnover by activating phos-

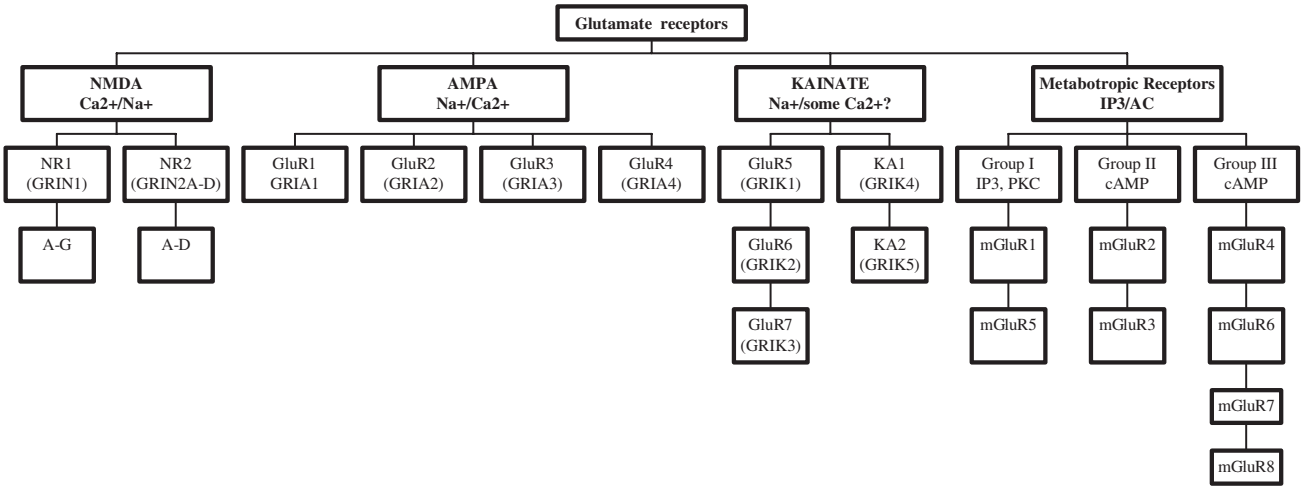

Fig. 1. The glutamate receptor families are schematically represented. Several receptor types have been characterised, cloned and sequenced (the identified genes are in parentheses). The transmembrane topology of glutamate receptors comprises three domains (M1, M3, and M4), plus a cytoplasm-facing re-entrant membrane loop (M2) (see Dingledine et al., 1999). The ionotropic family comprises the N-methyl-D-aspartate (*NMDA*), α-amino-3-5-methyl-4-isoxalepropionate (*AMPA*) and Kainate (*KA*) subfamilies. Dingledine et al. (1999) favours a tetramic protein model for the NMDA receptor, consisting of two NR1 and two NR2 subunits, modulating Ca^{2+} and Na^{+} conductance. AMPA receptors are also assembled by four subunits (*GluR1-4*), either alone or in various combinations, their functional properties depending on the subunit composition. AMPA receptors possessing the GluR2 subunit exhibit little Ca^{2+} permeability, while receptors lacking GluR2 show high Ca^{2+} permeability (Burnashev et al., 1996). The efficiency of NMDA receptors for transporting Ca^{2+} is approximately four times than that of AMPA receptors, probably because the pore of NMDA channels has multiple sites for Ca^{2+}, while that of AMPA receptor channels has only a single site (Wollmuth and Sakmann, 1998). The stoichiometry of the KA subfamilies is still unspecified, but appears to be complex, showing under certain circumstances some, but low, calcium permeability (see Burnashew et al., 1996). As for NMDA, AMPA receptor activation can be potentiated by various phosphokinases, including PKA, PKC, and calcium/calmodulin kinase II. AMPA and KA can be permeable to Ca^{2+}, but are tonically blocked at resting membrane potentials by cytoplasmic polyamine ions. Eight metabotropic glutamate receptor subtypes (*mGluR*) have been cloned from mammalian brain, classified into three subfamilies; group I, coupled to increases in phosphoinositide hydrolysis (IP3), and groups II and III coupled to inhibition of adenylate cyclase (*AC*)

pholipase C; (ii) the mGluR2 and mGluR3 subtypes are activated selectively by (2S,1′R,2′R,3′R)-2-(2,3-dicarboxycyclopropyl) glycine (DCG-IV) and 1-aminocyclopentane-1S,3R-cyclopentanedicarboxylic acid (ACPD), but only weakly by quisqualate, and inhibit cyclic AMP synthesis, and (iii) the mGluR4 mGluR6, mGluR7 and mGluR8 subtypes are potently activated by L-2-amino-4-phosphonobutyric acid (L-AP4), have a similar primary sequence and inhibit forskolin-stimulated cAMP formation (Nakanishi, 1992).

The ionotropic receptor subtypes exist in conjunction with various mGluR subtypes, but selective location in different neuronal compartments of the brain has also been described. Thus, while the NR1 subunit mRNA is ubiquitously expressed in almost all neuronal cells throughout the brain, the NR2A subunit is mainly expressed in neocortex, especially in layer V (Monyer et al., 1994), a region where many of the cortico-striatal projection pyramidal neurons are localised. Furthermore, NR2A and NR2B mRNA (Watanabe et al., 1992), as well as NR1 mRNA, and NR2A- and NR2B-like immunoreactivity (LI) are present in the neostriatum (Laurie and Seeburg, 1994; Standaert et al., 1994). In the majority of the cases, NR1 and NR2A and NR2B mRNA are observed in medium-sized spiny neurons containing the neuropeptide enkephalin (Laurie and Seeburg, 1994; Landwehrmeyer et al., 1995; Standaert et al., 1994), but also, although at lower levels, in somatostatin and cholinergic interneurons, which in addition contain NR2D mRNA (Landwehrmeyer et al., 1995). GluR1, and GluR2/3 receptor subtypes are expressed by medium-sized spiny efferent neurons and by parvalbumin positive interneurons (Chen et al., 1998), whereas the GluR4 subtype is expressed only by interneurons (Bernard et al., 1997; Kwok et al., 1997; Martin et al., 1993). Furthermore, high and intermediate levels of GluR2- and GluR3-LIs are found in enkephalin and calbindin positive neurons (Chen et al., 1996; Ghasemzadeh et al., 1996; Sato et al., 1993). Intense GluR5-7-LIs are present throughout the neostriatum, but without a clear neuronal segregation (Chen et al., 1996). However, GluR5 mRNA is highly expressed in the islands of Calleja, ventral pallidum and pars compacta of the substantia nigra, and GluR7 mRNA is highly expressed in the ascending nigrostriatal and mesolimbic dopaminergic neurons (Bischoff et al., 1997). Furthermore, there is evidence indicating extensive co-localization of GluR2 and GluR3 and GluR5-7 subunits (Ghasemzadeh et al., 1996).

mGluR3 mRNA is highly expressed in the neocortex and neostriatum, both in neuronal and glial cells (Ghasemzadeh et al., 1996; Ohishi et al., 1993; Petralia et al., 1996; Tanabe et al., 1993). mGluR5 is found at high levels in the neostriatum (Ghasemzadeh et al., 1996), mainly on enkephalin, substance P containing neurons and on interneurons and strionigral neurons of the dorsolateral region (Testa et al., 1994, 1995; Kerner et al., 1997; Tallaksen-Green et al., 1998). There is evidence for an intense mGluR5-LI in the neocortex and neostriatum, with both a pre- and postsynaptic location (Romano et al., 1995). A similar pre- and postsynaptic distribution has been reported for mGluR2- and mGluR3-LI (Petralia et al., 1996). Indeed, it has been shown that the intensity of mGluR2 and GluR3 immunoreactivity is decreased following decortication, suggesting a location on cortico-striatal terminals (Testa et al., 1998).

Due to its ubiquitous occurrence in the brain, glutamate and its receptors are crucially involved in several disease states. Overstimulation of glutamate receptors destroys the neurons bearing these receptors (excitotoxicity). Excitotoxicity plays a role in acute neurodegeneration (Kostrzewa, 1998; Sonsalla et al., 1998) and glutamate receptor-antagonists are promising drugs to reduce excitotoxic damage (Danysz et al., 1998).

Glutamate plays also a crucial role in several basal-ganglia diseases, especially in Parkinson's disease. Several lines of evidence indicate direct and indirect interactions between dopamine and glutamate in the basal ganglia of mammals (Calabresi et al., 1997; Meltzer et al., 1997; Zigmond et al., 1998; Chéramy et al., 1998; Herrera-Marschitz et al., 1998). NMDA-receptor-antagonists have psychomotor stimulant activity and effectively counteract parkinsonism symptoms in rats and monkeys (Carlsson and Carlsson, 1989; Schmidt, 1998; Ossowska et al., 1998; Starr, 1998). NMDA receptor-antagonists may also prevent the development of dyskinesias (Verhagen Metman et al., 1998).

It has been shown in primates that dopamine deafferentation induces an overactivity of glutamatergic neurons of subthalamic and cortico-striatal pathways (Bergman, 1990). Furthermore, while striatal neurons discharge spontaneously at a very low rate, their firing is increased following a 6-hydroxydopamine (6-OHDA) lesion. This increase in firing is blocked

by AMPA, but not by NMDA receptor antagonists (Calabresi et al., 1993).

A unilateral 6-OHDA lesion can produce short- and long-lasting changes in ionotropic and metabotropic receptor subtypes (Wüllner et al., 1994a,b). In our laboratories, we have found that a 6-OHDA lesion produces specific changes in several cortical and striatal neuron populations expressing markers for amino acid synthesis (Lindefors et al., 1989), and in a subpopulation of striatal neurons that is labelled with antibodies raised against aspartate (Pettersson et al., 1996). Furthermore, the dopamine D1 receptor agonist SKF 38393 (Setler et al., 1978) reduces the expression of glutamate receptor subtypes mGluR1,3,5 and NR1, but increases the expression of NR2B levels, indicating a complex interaction between dopamine and excitatory amino acid systems. The role of metabotropic glutamate receptors in Parkinson's disease is further investigated, promising new therapeutic opportunities (Wolfarth et al., 2000).

Other disease states in which glutamate receptors play a crucial role are schizophrenia (Ossowska et al., 2000; Svensson and Mathé, 2000), epilepsy (Rogawski, 2000) and addiction (Tzschentke and Schmidt, 2000).

The neurotransmitter role of aspartate is not yet clarified (see Herrera-Marschitz et al., 1997, 1998). Whenever glutamate is detected in the extracellular space of brain (Herrera-Marschitz et al., 1996), peripheral (Engidawork et al., 1997) tissue, guinea pig cochlea (Jäger et al., 2000), or even in organotypic cultures (Herrera-Marschitz et al., 2000), aspartate is also detected, although at lower concentrations. As glutamate, aspartate is released in an α-latrotoxin-dependent manner (Herrera-Marschitz et al., 1996), but, while both glutamate and aspartate levels are increased following the uptake blocker dihydrokainic acid, only glutamate levels are increased by L-trans-pyrrolidine-2,4-decarboxylic acid (Herrera-Marschitz et al., 1996), a selective glutamate uptake blocker (Bridges et al., 1991), suggesting a differential regulation. Furthermore, while glutamate has high affinity for all types of glutamate receptors, aspartate is selective for the NMDA receptor subtype, although with lower affinity than glutamate (Watkins and Evans, 1981; Patneau and Mayer, 1990). Using an antiserum raised against aspartate conjugated to key-hole-limpet hemocyanin, aspartate-positive neurons have been occasionally seen in the neostriatum of the rat (Snyder et al., 1993). We have found that the amount of aspartate-positive neurons is increased by metamphetamine, L-DOPA or SKF 38392 treatments, in particular when a D1-agonist is administered to animals with a unilateral 6-OHDA lesions (Pettersson et al., 1996). We have discussed the possibility that this striatal aspartate system is up-regulated under chronic L-DOPA treatment in Parkinson's disease, overstimulating NMDA-receptors and excitotoxicity (Herrera-Marschitz et al., 1998).

The participants of the Neurobiology Satellite of the Amino Acid congress in Vienna addressed the functional aspects of glutamate from different viewpoints. In Chapter I, the authors invited by Antonello Novelli and R. Andrew Tasker discuss the issue of excitotoxicity, a term originally proposed by Olney (1969), on the basis of studies demonstrating that L-glutamate is highly toxic to the brain. The papers describe basic research on the cellular basis of excitotoxicity, stressing the potential for new therapeutic strategies.

Amino acids are multifactorial biological entities, with neurotoxic and neuroprotective actions, according to cellular health status and intracellular milieu. This is the main issue of Chapter II, led by Richard M. Kostrzewa, John P. Kostrzewa and Ryszard Brus, where the authors provide insight into the newest developments on amino acids and novel approaches for treating Parkinson's disease and other neurodegenerative disorders. Viewed as a biologically inert amino acid in 1900, L-DOPA was later shown to be a metabolic precursor to the neurotransmitter dopamine, and ultimately as a consequence of O. Hornykiewicz' pioneering clinical studies in the 1960s L-DOPA has become the drug-of-choice for treating Parkinson's disease (Hornykiewicz, 2002). Often debated as a substance that accelerates the progression of Parkinson's disease, Kostrzewa et al. (2002) discuss the more-likely neuroprotective role of L-DOPA, which actively sequesters and inactivates reactive oxygen species including hydroxyl radical (Kostrzewa et al., 2000). In contrast, Kochman et al. (2002) focus on tyrosine, a metabolic precursor of L-DOPA, as playing a major role in regulating intracellular metabolism via the tyrosine radical intermediary which is also a potential cellular neurotoxin. Again, ongoing cellular activity has a major influence on the outcome of amino acid effects. Archer et al. (2002) describe studies on what is expected to be the next breakthrough in the treatment of Parkinson's disease, namely use of NMDA antagonists to enhance L-DOPA antiparkinsonian actions while simultaneously reducing the incidence of motor dyskinesias. That is-

sue is reinforced in Chapter III. Amino acid metabolism, gone 'astray' is the theme of the study by Walker et al. (2002), demonstrating that abnormal protein formation may catalyse further cellular deterioration – mechanism that could be important in Alzheimer's disease (senile plaques and tangles) and Parkinson's disease (Lewy bodies). These series of studies highlight a central duplicitous role for amino acids and proteins as active players in neurobiology and in neuropathological processs.

In Chapter IV and V, the authors invited by Thomas Tzschentke, and Stanislaw Wolfarth and Krystyna Ossowska, respectively, discuss glutamatergic mechanisms in different disease states. In Chapter IV, focus is given to glutamate-dopamine interactions associated to neuropsychiatric disorders, but also to drug dependence. NMDA and AMPA antagonism has a role in nociception, but kainate receptors play also a role in inflammatory and neuropathic pain (Chizh et al., 2002). In Chapter V, the authors discuss recent evidence dealing with drugs active on metabotropic receptors, which may be also useful in the therapy of neuropsychiatric disorders.

In Chapter VI, Hari Sharma and co-workers propose that injury to the CNS induces a series of complex neurochemical events that are progressive in nature, leading to widespread cellular and molecular alterations causing damage and/or cell death. Trauma to the CNS produces a breakdown of the microvascular permeability, leading to extravasation of serum proteins into the brain extracellular fluid compartment. Glutamate also contributes to membrane damage, probably via formation of free radicals and nitric oxide, as well as other neurochemical agents regarded as endogenous *neurodestructive* agents. However, apart of *neurodestructive* agents, a large number of other compounds are also released in the CNS following trauma, including immunomodulators, growth hormone and growth factors, acting as endogenous *neuroprotective* agents.

In Chapter VII, Olga Golubnitschaja and her co-authors present evidence demonstrating that molecular imaging of ischemia and angiogenesis provides insights into mechanisms of disease initiation, allowing early non-invasive diagnostic and preventive treatments.

The Satellite on Neurobiology has been again an opportunity to discuss new developments related to the role of amino acids in the CNS, and novel targets for therapeutic strategies. Therefore, the Editors would hereby like to acknowledge the support given by Merck KGaA, Darmstadt; Knoll AG, Ludwigshafen; Grünenthal GmbH, Aachen, Germany; Merck Sharp & Dohme Research Laboratories, Harlow Essex, UK; Novartis Pharma AG, Basel, Switzerland; Pfizer Global Research and Development, UK, Pharmacia & Upjohn, UK. Springer-Verlag Wien New York is also kindly acknowledged for making possible to prepare this Special Issues series in the journal *Amino Acids*. B. D. K. was supported by the DFG (KR-831/3-1). R. M. K. Was supported by NIH grant NS 39272. M.H.-M. would like to thank to the support by FONDECYT-Chile (grant N° 1000626).

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