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Amino Acids

Introduction: Signaling in neurodegeneration (Chapter 2)

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When introducing contributions to a recent session on Signaling in Neurodegeneration, it is impossible not to think that it is almost 50 years since the initial observations of Lucas and Newhouse (1957), yet investigation of glutamatergic neurodegeneration is still one of the most important topics in neuroscience. Understanding the role(s) of glutamate within the brain has implications in almost every field of neuroscience, including neurology, neuropsychology and psychiatry, from development to aging. It is, therefore, impossible to adequately represent the breadth and impact of this field in a single symposium or single collection of manuscripts. Instead, we have chosen to present four papers that deal with glutamatergic signaling at different levels of nervous system function; namely, characterization of the genome, molecular events at the cell membrane, interactions between glutamate release and intracellular messengers, and effects at the level of the intact animal. Each is important for understanding the complex relationship between glutamatergic signaling, toxicity and neurological disease.

The paper by Lipsky and colleagues describes sequence variation among the genes encoding for ionotropic glutamate receptors (IGRs). By combining high throughput screening with the power of bioinformatics applied to public and private domain databases, the authors describe how IGR sequences are both fundamentally conserved across phylogeny, even to the point where human genes are identifiably similar to those of plants. At the same time, their analyses also identify sequence variants within the human genome that might have considerable influence on neurobehavioural expression and human disease. The authors confirm that the three pharmacologically defined groups of IGRs are encoded by at least 6 gene families (1 AMPA, 2 kainate, 3 NMDA) and demonstrate that this configuration has been conserved throughout evolution. By focusing on the three NMDA receptor genes (GRIN1, GRIN2B and GRIN3) in an ethnically and clinically diverse group of individuals, however, they go on to describe a number of single nucleotide polymorphisms (SNPs) that may correlate with changes in NMDA receptor function that are linked to behavioural phenotypic diversity. This powerful combination of new sequencing technologies and ''data-mining'' is creating a wealth of opportunities for guiding future investigations of glutamate receptor function both *in vitro* and *in vivo* as described in the subsequent three papers in this series.

The second paper, by Cupello and coworkers, explores calcium signaling by providing state-of-art information on the dynamics of intracellular calcium following the activation of NMDA receptors and voltage sensitive calcium channels, with particular attention to their correlation with the functioning of $GABA_A$ receptors. In this respect it is worth noting that our current growing knowledge of the organization of cellular structures such as receptors and ion channels, in microdomains (Husi and Grant, 2001) favours the idea of a reciprocal modulation of the activity by such structures. Thus, the results obtained by Cupello and coworkers, both in the current, and previous papers, strongly suggest that clusters of NMDA and $GABA_A$ receptors are closely located along the neurites of cultured granule cells. This proximity allows for a calcium-mediated NMDA receptor control of chloride influx. The absence of an effect on $GABA_A$ receptor function on calcium entering the neurons following depolarization, affords further support for this idea since: 1) calcium concentration appears to increase mainly in the cell body where $GABA_A$ receptors are fewer, and 2) calcium influx following depolarization is short lived in neurites, making it less likely that significant

amounts of calcium will migrate to the clusters of $GABA_A$ receptors. Of course, it goes without saying that a full understanding of signaling interactions between NMDA and $GABA_A$ receptors will be of great importance for the future treatment of excitatory amino acid-related disorders.

Building on this theme of investigating the properties of glutamate receptors in relation to single cell function, the paper presented by Novelli and coworkers is focused on characterizing the pharmacological properties of the drug nefopam. These authors show that nefopam prevents the release of excitotoxic amounts of endogenous NMDA receptor agonists following the selective activation of L-type voltage sensitive calcium channels. In addition to the obvious intrinsic value of this work, the paper also relates well to the theme of the session in several ways, including:

1) several neurological/neurodegenerative disorders such as epilepsy and amyotrophic lateral sclerosis have been associated with an excessive release of endogenous excitatory amino acids (Cluskey and Ramsden, 2001; Vajda, 2002). Because the available drugs often fail to provide satisfactory control of the disease, there is a need for new therapeutic agents. Clearly, the discovery of novel properties related to the control of excitatory amino acid release for currently approved drugs, represents a considerable advantage for the timely introduction of new and much needed therapies.
2) some drugs that are used for both neurological/neurodegenerative disorders and neuropathic pain have proven to be useful in the control of bipolar psychiatric disorders. This may be the case for nefopam as well, due to its structural and pharmacological analogies with drugs such as carbamazepine and lamotrigine.
3) a large amount of evidence has accumulated in the last 20 years both in favor and against a role of calcium in excitotoxic neurodegeneration (Novelli et al., 2004). Among calcium-activated pathways involved in excitotoxic signaling, the production of nitric oxide has received particular attention because of the association of nitric oxide synthase with the NMDA receptor (Novelli et al., 2004). Less attention has been dedicated to the role of nitric oxide in neurodegenerative processes resulting from stimulation of ionotropic non-NMDA receptors. Thus, the results obtained by Novelli and colleagues in the present paper are important in suggesting that the formation of nitric oxide following stimulation of non-NMDA receptors with domoic acid, does not contribute to neurotoxicity.

Finally, the paper presented by Tasker and coworkers expands upon this theme of an interplay between NMDA and non-NMDA receptors, but uses a whole animal model in which brain development and learning are coupled with the actions of excitotoxic agents. Building on some previous work from this lab (Doucette et al., 2000; Doucette et al., 2003) the authors chose to study the effects of low doses of the excitotoxin domoic acid on an implicit learning paradigm during early postnatal rat development. Two aspects of this study are worth mentioning: 1) low doses of domoic acid, an agonist of ionotropic non-NMDA receptors, have been chosen in order to study the potential risk of exposure to this drug during development, and 2) classical conditioning is a form of implicit learning that has been recently shown to depend upon activation of excitatory amino acid receptors, namely NMDA receptors (Lincoln et al., 1988; Weldon et al., 1997; Mickley et al., 2000). The work presented establishes that exposure to doses of domoic acid sufficiently low to reasonably provide the selective activation of kainate receptors, stimulates the release of endogenous NMDA receptor agonists without inducing neurodegeneration. Furthermore, such repeated stimulation of NMDA receptors allows the development of classical conditioning when paired to an olfactory stimulus. Thus, exposure to domoic acid may have not only produced toxicity at high concentrations, but also has a nootropic effect at low concentrations that is probably mediated by the activation of kainate receptors. While such findings are particularly important to understanding the physiologic role of kainate receptors, they also stimulate novel questions about the role of kainate receptors in psychiatric disorders such as schizophrenia, where alterations in implicit learning are well known.

Thus, the four papers in this session encompass the full spectrum of neurobiological research; from genes to behaviour in an attempt to study the role(s) of glutamate and glutamate receptors in neural signaling. Although very different approaches have been applied to the questions at hand, there is a quite remarkable commonality to the conclusions, thereby confirming the value of interdisciplinary approaches to the study of neurobiology and neurodegeneration.

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