

Excitatory amino acids in epilepsy: from the clinics to the laboratory

Editorial

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Was Socrates suffering from epilepsy? A recent article presents evidence in favor of such a hypothesis based on critical reading of the writings of Plato and Xenophon in light of current knowledge about the disease (Muramoto and Englert, 2006). We now know many things about epilepsy, from the clinical presentation to the molecular basis of brain dysfunction, but there is still much more to learn and discover. However, when organizing a session on the role of excitatory amino acids in epilepsy, it should be remembered that one of the first physicians to believe epilepsy was a disease caused by an altered “molecular” mechanism was Hippocrates of Cos, who vehemently rejected any etiological explanation based on spiritual causes (Hippocrates, 1923). Apparently, during his traveling looking for the wisdom of other cultures, the young Hippocrates met Democritos of Abdera, who is unanimously considered to be the father of atomism and of the molecular movement. Hippocrates was much impressed by his ideas on perception, and were he alive today, Hippocrates would possibly be one of the prominent investigators on the field of epilepsy. As such, we decided to dedicate our session to the Hippocratic vision of integrating clinical and molecular medicine by having a clinical neurologist introducing the disease and its implications in neuropsychology and psychiatry, from development to aging. Then facing the impossibility to adequately represent the breadth and impact of this field in a single short symposium or single collection of manuscripts, we have chosen to have four contributions covering four questions: developmental changes following EAAs stimulation, role of excitatory-

inhibitory neurotransmission, endogenous mechanisms of neuroprotection, and mechanisms of action of new and old anticonvulsants.

The contribution by Dr. Marini and colleagues (Marini et al., 2007) focuses on the molecular mechanisms that control the transition from an excitatory to an excitotoxic role for glutamate, and how this may play an important role in controlling the rate of progressive neurodegeneration in the brain of epileptic patients undergoing seizure activity. An important process involved in protecting the brain is known as ischemic preconditioning. This phenomenon is believed to take place in the brain after mild ischemic insults and to protect from neurodegeneration during further ischemic insults that occur within a defined amount of time (Kirino, 2002). In the field of epilepsy a similar process is known as epileptic tolerance, where a mild epileptic insult protects neurons against both status epilepticus and ischemia, and hence is considered a form of cross tolerance (Plamondon et al., 1999). The molecular mechanisms underlying preconditioning neuroprotection are still poorly understood, but appear to include an important role for BDNF and several MAP kinases following activation of NMDA receptors. The work presented organizes the information available so far, and points out the open questions.

Beside NMDA receptors, kainate receptors are also believed to play an important role in epilepsy. The work presented by Dr. Maria Braga and colleagues (Aroniadou-Anderjaska et al., 2007) points out our actual knowledge of the mechanisms regulating neuronal excitability in the

amygdala, a crucial area in epilepsy. In particular, the markedly high expression of GluR5 KRs in the basolateral amygdala (BLA) may be a clue that these receptors play a prominent role in both the physiology and the pathology of the amygdala by modulating the synaptic release of GABA. Interestingly, the work of Dr. Braga also integrates in the facilitation of GABA release via presynaptic α_{1A} adrenergic receptors. This mechanism may significantly underlie the antiepileptic properties of norepinephrine. Notably, the α_{1A} adrenoceptor-mediated facilitation of GABA release is severely impaired by stress. This stress-induced impairment in the noradrenergic facilitation of GABA release in the BLA may underlie the hyperexcitability of the amygdala in certain conditions, and may explain the stress-induced exacerbation of seizure activity in epileptic patients.

Building on this theme of investigating the properties of glutamatergic neurotransmission, the paper presented by Dr. Tasker and coworkers (Doucette et al., 2007) 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, 2003; Tasker et al., 2005) the authors chose to study the effects of low doses of the excitotoxin domoic acid, administered during early postnatal development, on both cognition and emotionality in the adult rat. Disturbance of both cognitive function and emotionality are common in epileptic patients and are also major complications of anti-epileptic drug therapy. This newest paper from the Tasker lab not only reports on subtle changes in cognitive function in this new developmental rat model of epilepsy, but shows clearly that the effects are gender-specific. While such findings are particularly important to understanding the physiologic roles of kainate receptors, they also stimulate novel questions about risks of exposure to environmental toxins and food contaminants early during life on the development of epilepsy in adult age. Most current regulatory limits for contaminants in food are based on findings in adult animals and humans, but clearly the developing brain is exquisitely sensitive to insult even in the absence of immediate clinical signs. The study also raises the spectre that some of the complications in epilepsy, might manifest differently in males and females, which may suggest a need for more gender-based therapies.

Finally, the paper presented by Novelli et al. (2007) describes an effective interdisciplinary collaboration to use both *in vitro* and *in vivo* techniques to compare the pharmacological and behavioural properties of the drug

nefopam with those of established anticonvulsants such as carbamazepine. These authors show convincingly that in cultured neurons, nefopam prevents the release of excitotoxic amounts of endogenous NMDA receptor agonists following the selective activation of voltage sensitive sodium channels, at concentrations lower than those required by carbamazepine. In animals, nefopam effectively protects against maximal electroshock-induced seizures in mice, and shows a behavioral profile similar to carbamazepine. Furthermore, nefopam protects against convulsions induced by isoniazide, a glutamic acid decarboxylase inhibitor. 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) clinically, the available drugs for treating the symptoms of epilepsy often fail to provide satisfactory control of the disease, and new therapeutic agents are needed. New drug development, however, is both costly and time consuming. This paper clearly demonstrates that drugs that are already available for conditions other than epilepsy, may be an interesting alternative to totally new drugs.
- 2) Nefopam is currently commercialized as an analgesic drug, and it has recently been shown to be effective against neuropathic pain in animal models. The structural and pharmacological analogies and differences between this drug and carbamazepine may be of interest for modeling the interaction of these two drugs with their common targets, and may be useful for the development of new molecules with anticonvulsant activity.

Thus, the four papers in this session encompass the full spectrum of research on epilepsy; from single cell to whole animal behaviour in an attempt to understand the role of glutamatergic neurotransmission in normal and abnormal brain functioning. In addition, however, they all attempt to explain some of the clinical features of epilepsy, and to open up new options for effective therapeutic approaches to dealing with this debilitating disease.

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