Kainic Acid and Temporal Lobe Epilepsy

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Kainic Acid and Temporal Lobe Epilepsy: Two Decades of Progress

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Animal models of epilepsies have been instrumental in determining the mechanisms of epileptogenesis and its relation to brain damage. In the field of temporal lobe epilepsies, studies using kainic acid have provided specific answers to a series of questions that have been debated for over a century, including: are the seizures the cause or the consequence of the damage? Does activity per se lead to cell loss and if so how? Is the brain permanently modified after brief seizures? In that respect the history of research on kainate is quite instructive on the tortuous routes that lead to progress in science. Kainic acid ("the dragon of the sea") was isolated in the early 1960s from the seaweed *Digena simplex* extensively used in post-war Japan to eradicate ascariasis and found to produce a potent depolarization of cortical neurons, an effect mediated by receptors that are activated by endogenous glutamate.\(^1\) J. Olney and colleagues then found that glutamate and its analogues - most notably kainite - induce excessive excitation of neuronal somata that leads to cell death: "the "excitototoxic" concept.\(^2\) Kainate was then used for many years as a tool to destroy neurons but not fibers *en passant*. Subsequently, a link between seizures and epilepsies was made when intra-cerebroventricular\(^3\) or intra-amygdaloid\(^4\) injections produced a seizure and brain damage syndrome reminiscent of ammon's horn sclerosis (see Figure1A-B).
**Figure 1:** Kainate treatment produced in Wistar rats a dramatic degeneration of hippocampal neurons and a reactive sprouting of granule cell axons. A, B. MAP-2 staining of hippocampal sections from control (A) and kainate-treated (kainate was injected into the amygdala; B) rats. Note the neuronal loss of hilar (H) and CA3 pyramidal neurons (arrows) induced by this convulsant. C, D) Photomontage of calbindin immunostained dentate gyrus sections (in green) and camera-lucida reconstructions of Golgi impregnated granule cell bodies and dendrites (in white) and axons (the mossy fibres, in yellow) from control (C) or kainate-treated (D) rats. The axons of granule cells sprout after kainate, course the granule cell layer (G) and end within the inner molecular layer (m). Figure by Alfonso Represa.

**Seizures and brain damage: the chicken and the egg**

Studies using this model showed that seizures are the cause but also the consequence of the damage since: i) blocking the seizure with diazepam prevents the "distant " hippocampal damage; ii) the severity of epileptiform activity strongly correlates with the extent of the damage in the CA3 region of the hippocampus; iii) chronic destruction of hippocampal inputs prevent the damage and iv) measures of the local hippocampal blood flow and oxygen consumption during the seizures in vivo indicate that the damage is not due to an imbalance between supply and demand. However, seizures are also a consequence of the damage, since, following status, fibers sprout and establish novel synapses, including aberrant excitatory ones that contribute to the epileptogenicity of the tissue. This form of reactive plasticity concerns the mossy fibers that innervate the vulnerable CA3 pyramidal neurons (Figure 1 C-D) and also CA1 pyramidal neurons, where electrophysiological recordings from soma and dendrites show a massive increase of glutamatergic spontaneous activity indicating that newly formed synapses are functional. Therefore, seizures can induce distant damage through neuronal hyperactivity, triggering a cascade of events that lead to neuronal cell loss in vulnerable regions and followed by excitatory neosynapse formation.

**A molecular scenario that links the seizures with the formation of novel aberrant synapses**

Recurrent seizures are associated with a large CA$^{2+}$ influx, long-lasting change in synaptic efficacy-like classical LTP, and by a sequence of events that include as many as 1000 genes responsible for sprouting and neosynapse formation, including immediate early genes, growth factors genes, glial markers, cytoskeletal proteins, cell adhesion, etc. This sequence constitutes one of the best models of activity-induced neosynapse formation in the adult brain.

**Failure of inhibition in epilepsy: revisiting an old debate**

A reduction of GABAergic inhibition has always been thought to provide a rational explanation for seizure generation. However, a direct test of the electrical behaviour of all the elements involved, including the dendrites and somata of the principal cells and various types of interneurons in slices obtained from kainite-treated animals, show that things are not so simple. First, dendritic projecting interneurons - notably the ones containing somatostatin that project to the distal part of the apical dendrites - degenerate and there is a permanent reduction of spontaneous GABAergic tone. In contrast, interneurons that innervated the cell bodies are not destroyed by the status and there is an increase of the inhibitory tone. This is due to the formation of novel glutamatergic synapses on interneurons. Thus, the failure of inhibition concerns primarily dendritic inhibition, although alterations of axo-axonic interneurons have been reported: inhibition is operative in the epileptic cortical network but its mode of operation is altered, thus modifying the conditions of generation of synchronized activities.

**Kainate receptor subunits: one excites, one inhibits**

Using agents that differentiate AMPA from kainate receptors, several "kainatergic" synapses have been identified and, using molecular biology techniques, several kainate receptor subunits have been cloned. Two subunits are of particular interest: GluR5 enriched in interneurons and GluR6 enriched in mossy fiber synapses. Activation of the former enhance the inhibitory drive on the principal cells de facto increasing inhibition and acting to reduce seizure threshold, whereas the
GluR 6 enriched mossy fibers are essential for seizure generation.\textsuperscript{10} Thus, kainate both generates seizures and also increases seizure threshold by means of two different receptors via two populations of neurons. This dual action is also in line with the central role of interneurons in the generation of synchronized activities such as seizures: seizures and kainate do not simply reduce seizures - the effects will depend largely on the synchronizing capacities of the network and the selective activation of neuronal populations.

**Kainatergic synapses: the ultimate generators of rhythmic activity**

Another dogma that recent studies have alleviated is the notion that kainate receptors are localized in non-synaptic distal sites and primarily activated by the excessive release of glutamate. This was largely based on the long kinetic of kainatergic EPSCs evoked by bulk stimulations that activate many bundles of axons and synapses. More recent studies suggest that miniature EPSCs and minimal PSCs activated by single axons generate PSCs with time constants compatible with classical synaptic data and close to those of receptors expressed in vitro.\textsuperscript{11} Thus, kainate receptors represent a classical subtype of glutamate receptors that participates in ongoing synaptic activity. In fact, quantitative data in hippocampal interneurons and CA3 pyramidal neurons suggest that they provide over half the charge provided spontaneously by the various glutamatergic synapses: more than AMPA, the classical excitatory receptor. This is very surprising and adds to the multiple facets of a receptor. It clearly suggests that this family of receptors, which has not been added to the family of glutamate receptors to generate seizures, exerts a unique role in generating synchronization in cortical circuits. Seizures are a side-consequence of this, due to the fundamental capacity of limbic structures to generate patterns and corresponding behaviours. It remains to understand fully what role kainate receptors exert in physiological conditions.

This story illustrates how, starting with a simple natural glutamatergic agonist, one ends with a major source of unique excitatory synapses that, thanks to their distribution and properties, play a central role in generating oscillations and en passant have helped in the understanding of epilepsies.

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