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Neurotoxicity of kainate and the inactivation of L-glutamate *in vivo*

J.C. BORNSTEIN, D.R. CURTIS, G.A.R. JOHNSTON & D. LODGE

Department of Pharmacology, John Curtin School of Medical Research, Australian National University, Canberra, ACT, Australia

Destruction of neurones by kainic acid and related 'excitotoxic' amino acids (Olney, 1978) is partly dependent on intact excitatory pathways in which glutamate is likely to be the transmitter (McGeer, McGeer & Singh, 1978). The neurotoxicity of kainate may thus depend on excessive membrane depolarization by a combination of a direct action of this potent excitant and an increased effectiveness of synaptically released L-glutamate. Since kainate and the derivative dihydrokainate, which is only a weak excitant of neurones, inhibit the high affinity uptake of L-glutamate to a similar extent (IC_{50} 302 ± 30 and 176 ± 10 μM respectively) (Johnston, Kennedy & Twitchin, 1979), and kainate is known to potentiate the action of L-glutamate on cortical neurones (Shinozaki & Shibuya, 1976), interference with L-glutamate transport may contribute to the neurotoxic effects of kainate.

Using microelectrophoretic techniques, experiments were performed on 7 cats anaesthetized with pentobarbitone to study the specificity of the effects of kainate and dihydrokainate on the excitation of spinal neurones by a variety of excitant amino acids and acetylcholine.

Dihydrokainate enhanced the action of L-glutamate, L-aspartate, D-glutamate and L-homocysteate but had little or no effect on the actions of D-homocysteate, kainate, N-methyl-D-aspartate and acetylcholine. Since only the substances in the 'enhanced' group are likely to be actively transported into neuronal tissue, these results suggest the importance *in vivo* of dihydrokainate-sensitive uptake systems for the neurotransmitters L-glutamate and L-aspartate.

Attempts to demonstrate a differential effect of kainate on the firing of neurones by L-glutamate, NMDA and acetylcholine were not successful largely because in concentrations likely to influence the uptake of L-glutamate, kainate produced excessive excitation followed by inactivation. At lower doses the effects of L-glutamate, NMDA and acetylcholine were all enhanced to a similar extent. Nevertheless, it seems likely, from *in vitro* observations and the *in vivo* action of dihydrokainate described here, that following injection into the brain (usually 1–2 μl of 1–10 mM soln.) kainate would enhance the effects of L-glutamate and L-aspartate and that this action would contribute to its neurotoxicity.

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