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Rapid communication

QUINOLINIC ACID: A POTENT ENDOGENOUS EXCITANT AT AMINO ACID RECEPTORS IN CNS

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It seems likely that a dicarboxylic amino acid such as glutamic acid or aspartic acid is a synaptic transmitter in the mammalian central nervous system (Curtis and Johnston, 1974). Antagonists have recently been developed which suggest the existence of at least two kinds of receptor for these amino acids, one preferentially activated by N-methyl-D-aspartate (NMDA), the other by quisqualic acid (Watkins et al., 1981) but the latter two excitants are not known to occur in the CNS. We now report that the endogenous compound quinolinic acid (2,3-pyridine dicarboxylic acid) is also a potent excitant of neurones in the rat brain and that it may act preferentially on NMDA receptors.

Experiments were conducted on neurones in the cerebral cortex of male rats anaesthetised with urethane (1.5 g/kg). Compounds were applied by microiontophoresis from 7-barrelled micropipettes filled immediately before use with 10 or 25 mM solutions of the compounds. Unit activity was recorded through a separate single electrode glued alongside the iontophoresis assembly. The relative potency of agonists was assessed by adjusting the iontophoretic dosage to obtain approximately equal sized responses and then taking the ratio of the effective doses in nanocoulombs. This ratio was determined for each cell studied, all the agonists being subjected to the same retaining current of 0 to 10 nA. Care was taken to ensure that all responses were submaximal, with no sign of overdepolarisation.

The similarity in the nature and time course of excitatory responses to NMDA, quisqualate and quinolinic acid may be seen in fig. 1. Quinolinic acid excited all of 54 neurones tested, with ejecting currents of 20 to 80 nA for about 5 to 10 sec.

The comparison of ejecting currents for comparable responses indicated that quinolinic acid was about as potent as glutamate and aspartate, about one quarter as potent as NMDA and one tenth as potent as quisqualate.

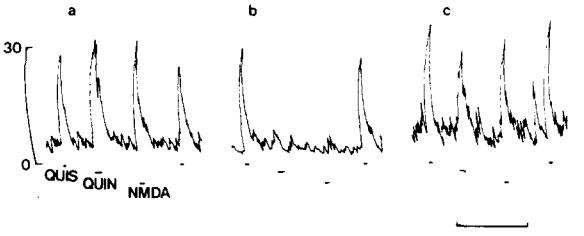

Fig. 1. Record of the firing rate of a neurone in the cerebral cortex excited by the iontophoresis of quisqualic acid, 16 nA (QUIS), quinolinic acid, 22 nA (QUIN) and NMDA, 20 nA. Panel a shows a series of control responses; b was taken 2 min after beginning an ejection of 2-amino-5-phosphono-valeric acid, 6 nA. Note the blockade of quinolinic acid and NMDA, but not quisqualic acid. Panel c shows recovery, 2 min after b. Ordinate: firing rate in spikes/sec. Time bar: 1 min.

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The selective NMDA antagonist (−)-D-2-amino-5-phosphonovaleric acid (2APV) (Perkins et al., 1981) produced a rapid abolition of responses to NMDA and quinolinic acid while quisqualate responses were unchanged (16 or 18 cells) (fig. 1.) The antagonist glutamic acid diethylester (GDEE) which in the spinal cord is more effective as a quisqualate and glutamate antagonist than as an NMDA antagonist proved to be less specific in the cortex and selectively reduced responses to quisqualate on only 9 of 24 cells. Quinolinic acid responses were reduced in parallel with quisqualate on 5 of these.

Quinolinic acid is clearly a potent excitant of rat cortical neurones, comparing well in potency with the other compounds occurring naturally in the CNS (L-glutamate and L-aspartate).

Like L-glutamate and L-aspartate, quinolinic acid may activate both the NMDA and quisqualate type of amino acid receptor, as antagonists at both receptors were able to block quinolinate responses. However, in view of the far greater ease of blockade by 2APV rather than GDEE we would suggest further examination of the possibility that quinolinate may act preferentially on the NMDA receptor.

In view of the potency of the excitatory effect of quinolinic acid and its natural occurrence both in mammalian cells (Mahler and Cordes, 1971) and at the crustacean neuromuscular junction (Netherton and Gurin, 1980) where an excitatory amino acid or related compound have been suggested as the transmitter, it is possible that quinolinic acid may have an important role to play in neuronal excitation.

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