gesia with relatively little respiratory depression has previously been observed with, for instance, nalorphine (Keats & Telford 1966). The cardiovascular changes observed with meptazinol were notably a fall in heart rate with little change in arterial pressure and resembled those found with morphine in this study and with other analgesics of this type in the rat (e.g. Cowan et al 1977).

The convulsant effect of large doses of pentazocine has been reported both in animals and in man (Brogden et al 1973). It is possible that the large increase in respiratory frequency observed with pentazocine in these experiments could be a reflection of the convulsant effect and could tend to mask respiratory depressant changes in blood gases. It seems unlikely that a similar situation could exist with meptazinol as no change in respiratory frequency was observed with this drug and no signs of respiratory depression were seen at the lower, non-convulsant dose of meptazinol.

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Nuciferine and central glutamate receptors

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On the basis of theoretical considerations, and the result of in vivo and in vitro experimental studies, neuronal excitants chemically related to aspartate and glutamate appear to interact with different types of receptor site, some of which may interact with more than one class of agonist (Watkins 1978; Johnston 1979). The analysis of central excitant amino acid receptors is complicated, however, not only by regional and species differences and the difficulty of relating binding sites investigated under in vitro conditions to functionally significant receptors operating at synapses in vivo, but also by the probable innervation of many neurons by both aspartergic and glutamergic pathways (Curtis 1979). The degree of specificity of agonists and antagonists is thus of critical significance in both in vivo and in vitro investigations.

McLennan & Lodge (1979) have demonstrated that whereas the excitations of spinal interneurons and Renshaw cells (cats anaesthetized with pentobarbitone) by *N*-methyl-D- and -L-aspartate (NMDA, NMLA) and ibotenate were readily antagonized by D-α-aminoadipate (DαAA; Hall et al 1977; Biscoe et al 1977) and much less readily by L-glutamic acid diethylester (GDEE; Haldeman & McLennan 1972), excitations by L-glutamate and quisqualate were readily reduced by GDEE and much less so by DαAA. In contrast, excitation by kainate was almost insensitive to antagonism by GDEE and only slightly reduced by DαAA (see also Lodge et al 1978). A similar finding has been reported for rat thalamic neurons (McLennan & Hall 1978; Hall et al 1979). These and other observations suggest that whilst NMDA, NMLA and ibotenate may be selective agonists for L-aspartate receptors at which DαAA is an antagonist, L-glutamate and quisqualate may be more specific agonists than kainate for L-glutamate receptors which are antagonized by GDEE. On the basis of the reduction of certain synaptic excitations by GDEE (see Curtis 1979) these latter receptors may be those with which L-glutamate interacts as a synaptically released excitatory transmitter.

Recently Davies & Polc (1979) have reported that L-nuciferine (L-5,6-dimethoxyaporphine), previously found not to differentiate between the excitatory effects of L-glutamate and acetylcholine (ACh) on Renshaw cells in the rat (Duggan et al 1973) and cat (Curtis et al unpublished observations), depressed the excitation of feline Renshaw cells by ACh and kainate more than that by NMDA. Furthermore, the excitation of spinal interneurons by kainate was more sensitive to L-nuciferine than excitation by NMDA. This preferential reduction of excitation by kainate provides some support for proposed differences between receptors for NMDA and kainate, and for earlier proposals that L-nuciferine may selectively influence L-glutamate receptors in the cat cuneate nucleus (Hind & Kelly 1975), thalamus (Ben Ari & Kelly 1975; but see McLennan & Wheal 1976) spinal cord (Polc & Haefely 1977) and in the pigeon optic tectum (Felix & Frangi 1977).

In view of these results, the opportunity was taken to examine the selectivity of L-nuciferine as an antagonist of the excitation of spinal neurons by a range of excitant amino acids. The effects of 9-methoxyaporphine were also examined as this compound has previously been reported (as 2-methoxyaporphine; Curtis et al 1972) to diminish the effectiveness of both L-glutamate and L-aspartate as excitants of Renshaw cells more than that of acetylcholine, without distinguishing between excitation by the two amino acids. The experiments were performed on dorsal horn interneurons and Renshaw cells in lumbar segments of 5 spinal cats,

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anaesthetized with pentobarbitone sodium (35 mg kg^{-1}, i.p.), using conventional microelectrophoretic methods. The centre recording barrels of seven barrel micropipettes (overall tip diameters 4–6 μm) contained 3·6 M NaCl and the outer barrels aqueous solutions of L-glutamate Na (0·2 M, pH 7·5), quisqualate Na (5 mM in 165 mM NaCl, pH 7·5), kainate Na (5 mM in 250 mM NaCl, pH 7·5), NMDA Na (50 mM in 150 mM NaCl, pH 7·5), acetylcholine bromide (ACh, 0·25 M), L-nuciferine HCl (10 mM in 150 mM NaCl, pH 3·4) and 9-methoxyaporphine HCl (2 mM in 150 mM NaCl, pH 3·1). The excitants were ejected for fixed periods at regular intervals using a series of pre-programmed timers and with electrophoretic currents chosen to produce similar maximal rates of firing within the range of 40–80 spikes s^{-1}.

As in earlier studies, L-nuciferine often reduced the amplitude of extracellularly recorded action potentials of interneurons and Renshaw cells. In contrast to the finding of Davies & Polc (1979), however, the excitation of 7 interneurons by kainate was equally or less sensitive to antagonism by L-nuciferine than was excitation by NMDA. Excitation by either L-glutamate or quisqualate was even more sensitive to L-nuciferine than excitation by NMDA. Only with one interneuron was the firing induced by kainate reduced to a greater extent by L-nuciferine than excitation by NMDA, and the most usual sequence of the excitants, listed in order of *increasing* sensitivity to antagonism by L-nuciferine, was kainate, NMDA, quisqualate and L-glutamate. Results from one interneuron which illustrate this finding are shown in Fig. 1A–C.

A similar order was observed with 3 of 4 Renshaw cells, L-nuciferine reducing excitation by ACh to a similar extent as that by L-glutamate. The excitation by kainate of the fourth cell was more sensitive to L-nuciferine than that by either ACh or NMDA. With three of four other Renshaw cells not tested with NMDA, kainate or quisqualate, excitation by ACh and L-glutamate was similarly reduced by L-nuciferine, with the other cell L-nuciferine was more effective as an ACh antagonist.

Seven interneurons and 4 Renshaw cells were tested with 9-methoxyaporphine, and the results were similar

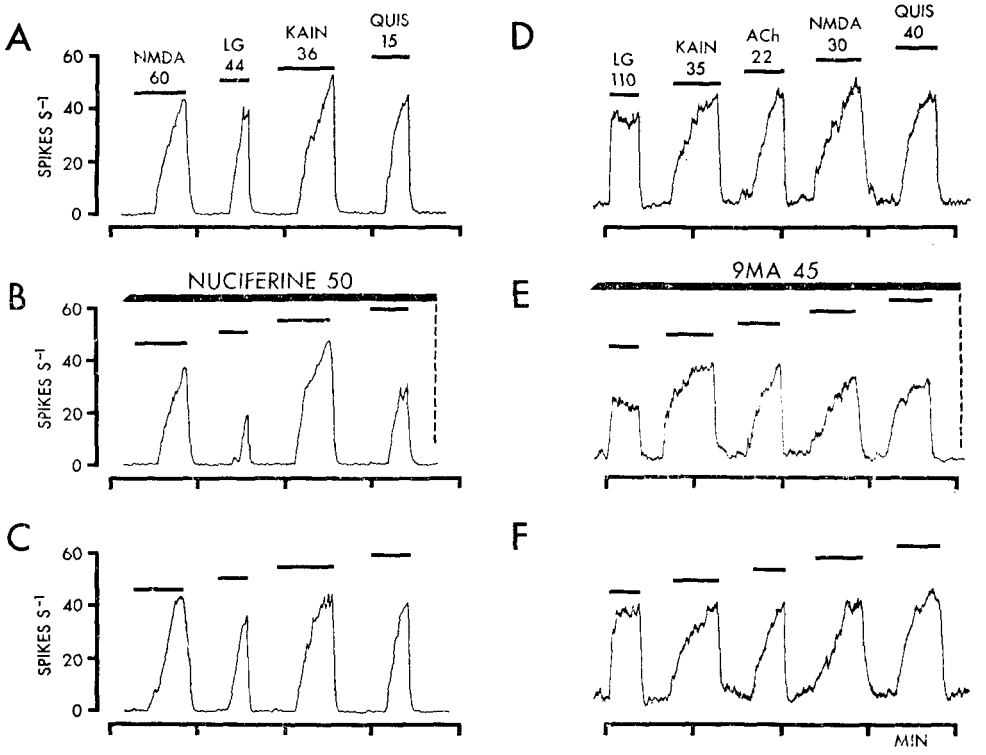

FIG. 1. Ratemeter records of the effects of nuciferine and 9-methoxyaporphine (9MA) on the chemical excitation of an interneuron (A–C) and a Renshaw Cell (D–F). The excitants were ejected electrophoretically for the times indicated by the horizontal bars using the indicated currents through barrels containing solutions, listed in the text, of *N*-methyl-D-aspartate (NMDA), L-glutamate (LG), kainate (KAIN), quisqualate (QUIS) and acetylcholine (ACh). A and D, control observations. B, during the administration of nuciferine (50 nA) which commenced 1 min earlier and ceased at the vertical broken line. C, 30 s after B. E, during the administration of 9MA (45 nA) which commenced 4 min earlier and ceased at the vertical broken line. F, 5 min after E. Ordinates: firing rate, spikes s^{-1} Abscissae: time, min.

to those discussed above. With each neuron the excitatory action of L-glutamate was reduced more than that of NMDA, and of the 7 upon which NMDA and kainate were compared, excitation of 6 by NMDA was reduced more than or equal to that by kainate. As with L-nuciferine the excitatory action of quisqualate was similarly or slightly less reduced by 9-methoxyaporphine than that of L-glutamate (9 neurons). 9-Methoxyaporphine also reduced the excitatory action of ACh on Renshaw cells, but slightly less than that of L-glutamate and quisqualate and either similar to or more than that of kainate. Results from one Renshaw cell are illustrated in Fig. 1D–F.

In these experiments the aporphines only rarely reduced the sensitivity of spinal neurons to kainate more than that to NMDA. Furthermore, excitation by L-glutamate and quisqualate was reduced to a greater extent than that by NMDA. These findings are in conformity with in vitro studies in which nuciferine (40 μM) inhibited the binding of L-glutamate more than that of L-aspartate to a hydrophobic protein fraction isolated from rat cerebral cortical synaptic membranes (Fiszer de Plazas & De Robertis 1976), and nuciferine and 9-methoxyaporphine (100 μM) did not significantly interfere with the sodium-independent binding of kainate to rat brain membranes (Johnston et al 1979). On the other hand, the present observations do not confirm those of Davies & Polc (1979) regarding the greater sensitivity to L-nuciferine of the excitation by kainate than by NMDA of spinal neurons in cats anaesthetized with pentobarbitone. In general terms they do support the conclusion that L-nuciferine may interact with L-glutamate receptors which, however, are not activated by kainate.

Ligand binding studies carried out in vitro in the absence of sodium ions suggest that kainate binds with relatively high affinity to only a small proportion of L-glutamate sites with which L-glutamate presumably binds in an extended conformation (Simon et al 1976; Johnston et al 1979; Johnston 1979). This finding, together with the present results, indicate that kainate, a conformationally restricted analogue of L-glutamate, should not be used alone as an excitant in evaluating the specificity of antagonists of L-glutamate receptors at excitatory synapses. Specific antagonists for naturally occurring excitatory amino acids are essential for further characterization and localization (synaptic, extrasynaptic) of the various types of receptor identified in vitro, although full correlation between in vivo and in vitro observations might not be achieved, especially given the limitations of microelectrophoretic methods for determining the nature of somatic and dendritic neuronal receptors (Curtis 1976; Lodge et al 1978).

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