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AMINO ACIDS AS NEUROTRANSMITTERS OF CORTICOFUGAL NEURONES IN THE RAT: A COMPARISON OF GLUTAMATE AND ASPARTATE

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1 The relative sensitivities to aspartate and glutamate of neurones receiving a corticofugal innervation were examined by microiontophoresis, and compared with the relative sensitivities of neurones not appearing to receive such an input.

2 On all the cells tested, glutamate appeared to be a more potent excitant than aspartate in terms of neuronal response size or effective dose.

3 DL-α-Aminoadipate (αAA) reduced the excitatory amino acid responses on all the neurones tested. On many of these cells a control excitation could be produced, by acetylcholine or hydrogen ions, which was in most cases unaffected by doses of αAA producing antagonism of amino acid excitation.

4 On 70% of the cells, aminoadipate showed no selectivity for aspartate compared with glutamate but a differential action, involving blockade of aspartate but not glutamate, was apparent on the other 30%.

5 Doses of αAA which selectively reduced responses to aspartate had no effect on short latency evoked spikes, but doses which also reduced responses to glutamate reduced the short-latency synaptic excitation induced by electrical stimulation of either the surface of the cerebral cortex, or of the pyramidal tracts in the medulla.

6 These findings suggest that corticofugal neurones having an excitatory action on cells in various parts of the brain may use an amino acid, probably glutamate, as a common neurotransmitter.

7 As no significant difference could be demonstrated in the potency ratios of glutamate:aspartate on monosynaptically activated cells compared with other cells, doubt is cast on the validity of drawing conclusions about transmitter identity from potency ratios alone, without the support of antagonist studies.

Introduction

On the basis of the marked sensitivity to L-glutamate shown by cortical neurones activated by the pyramidal tract, and the ability of antagonists of glutamate to block synaptically induced excitation, it was suggested that L-glutamate might be the excitatory neurotransmitter released by those corticofugal neurones forming the pyramidal tract (Stone, 1973; 1976).

Complementary evidence has been obtained by other groups to suggest that corticostriate fibres also release an amino acid, probably glutamate (Spencer, 1976; Divac, Fonnum & Storm-Mathisen, 1977; McGeer, McGeer & Singh, 1978). It is therefore possible that all cortical efferent excitatory axons utilize an amino acid transmitter.

With this background, the present study was designed with two aims. The first was to examine the efficacy of DL-α-aminoadipic acid as an antagonist of the excitatory amino acids and of synaptic excitation in the cuneate nucleus, the caudate nucleus and the cerebral cortex itself, the synaptic excitation being induced by stimulation of either the medullary pyramids or the cortical surface. It has been claimed (Biscoe, Davies, Dray, Evans, Francis, Martin & Watkins, 1977a; McLennan & Hall, 1978) that α-aminoadipate is a more specific antagonist of the excitatory amino acids than the hitherto used compounds such as glutamic acid diethylester and 1-hydroxy-3-amino pyrrolidone-2 (Davies & Watkins, 1973; Stone, 1976). The D-isomer of α-aminoadipic acid has been shown to be responsible for the antagonism (Biscoe, Headley, Lodge, Martin & Watkins, 1976; Biscoe *et al.*, 1977a; Biscoe, Evans, Francis, Martin, Watkins, Davies & Dray, 1977b; McLennan & Hall, 1978).

The second aim of this study was based upon the additional claim that α-aminoadipic acid shows a preference for blocking excitation produced by aspartate

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rather than glutamate (Biscoe *et al.*, 1977a, b). If this could be confirmed, then it might be possible to use a dose of α-aminoadipate which would specifically block aspartate to examine synaptic excitation by the pyramidal tract, and thus to detect any involvement of aspartate rather than glutamate as a corticofugal neurotransmitter. We have also estimated the relative excitant potencies of glutamate and aspartate on neurones receiving direct corticofugal fibres and on cells not thus characterized, in order to assess the validity of forming conclusions about transmitter identity on the basis of relative neuronal sensitivity (Duggan, 1974).

Methods

Male Porton Wistar rats weighing 250 to 350 g were anaesthetized with urethane (1.25 g/kg. i.p.) and then placed in a stereotaxic frame. Body temperature was maintained at 37 to 38°C by means of an automatically regulated heating blanket and rectal probe. An area approximately 4 mm square of cerebral cortex was exposed immediately anterior to the bregma suture, to allow access to the motorsensory cortex. In appropriate experiments, separate burr-holes were made over the parietal lobe to permit access to the caudate nucleus (co-ordinates AP 0; L 3.0; V 4.0–5.0 of Fifkova & Marsala, 1967) and over the cerebellum to permit dorsal access to the medullary pyramid as described previously (Stone, 1972). Stimulation of the cortical surface was effected by single anodal pulses of 0.1 ms duration applied via a silver ball electrode on the motor cortex, using a Grass S44 stimulator and photically coupled stimulus isolator. The ipsilateral pyramid was stimulated by a concentric bipolar electrode located at planes AP 12.0; L 0.5; V 8.5–9.5. Correct siting and adjustments of the electrode depth were made by observing the characteristic cortical evoked potentials produced by pyramidal stimulation (Stone, 1972).

The dura was removed from all exposed parts of the brain and, after positioning the appropriate electrodes, these areas were covered with a layer of 4% agar in saline to prevent cooling and drying and to reduce respiratory and vascular movements of the tissue.

For the microiontophoretic application of compounds, 7-barrelled micropipettes were used. The pipette tips were broken under microscopic observation to an overall diameter of 10 to 15 μm, and the barrels were filled with drug solutions immediately before use. The following solutions were used: L-glutamate sodium 0.2 M, pH 7.0; L-aspartate potassium, 0.2 M, pH 7.0; acetylcholine chloride, 0.2 M, pH 4.5; DL-α-aminoadipic acid, 0.05 M, adjusted to pH 7.0.

Iontophoretic ejection was effected by a Digitimer Neurophore Unit incorporating automatic balancing at the electrode tip. In this way current flow to ground and thus current artefact was minimized. When not being ejected, all compounds were subjected to a retaining current of 10 to 15 nA. In spite of the relatively large size of pipette tip used here, these holding currents seem to be sufficient to prevent changes of firing rate attributable to drug leakage. This conclusion is based on control experiments with glutamate or γ-aminobutyric acid (GABA), in which background firing was observed for periods of over 1 h.

Extracellular recordings of unit activity were made with single glass microelectrodes containing 1 M potassium acetate and having resistances of 1 to 8 MΩ at 1 kHz, fixed alongside the multibarrel pipettes (Stone, 1973). The tips of the recording pipettes were bent to an angle of approximately 20° during the pulling process to facilitate fixing them alongside the multibarrel. The tips were initially approximated by eye, and then under microscopic control. During this stage the electrodes were held together by Plasticine. Permanent fixing was then achieved with an epoxy resin. The approximation was always confirmed microscopically immediately before and after each experimental penetration. The recording electrode was arranged to project 5 to 20 μm beyond the multibarrel tip.

Unit activity was amplified by a Grass P511 amplifier and the spikes were then passed through a window discriminator, the output pulses of which were counted and displayed on a Grass polygraph. Spikes were simultaneously displayed on oscilloscopes and were also available for recording on magnetic tape and for on-line generation of post-stimulus time histograms.

Results

Identification of units

The characterization of units in the cerebral cortex which can be activated monosynaptically from the medullary pyramid has been described in a previous report (Stone, 1973). These units are primarily interneurones, though a small number of pyramidal tract neurones can themselves be excited synaptically. The interneurones are encountered infrequently on account of their low spontaneous firing rates and small spike size. Eight monosynaptically activated interneurones were encountered in the present study having latencies in the range 2.6 to 6.2 ms (mean 3.4). The initial spikes varied in latency by no more than 0.25 ms and would follow stimulus repetition rates between 15 and 45 Hz.

Criteria have previously been presented for identifying units in the cuneate nucleus activated monosynaptically from the cortical surface (Stone, 1976). Ten such neurones were recorded in the present experiments, with initial latencies of 2.2 to 4.4 ms (mean 3.1) and following stimulus frequencies of 25 to 80 Hz.

In the caudate nucleus, synaptic activity was evoked in 24 neurones by surface stimulation of the cortex. The responses to minimally effective single cortical stimuli consisted of 1 to 6 spikes. In the case of 16 of the caudate cells the initial spike appeared to be monosynaptic, as the spike latency varied by no more than 1 ms, and the spike would follow cortical stimulation at about 60 Hz. The latencies of these short latency spikes ranged from 2.2 to 10.6 ms (mean 4.8 ms). Although these latencies are quite long for monosynaptic spikes they are consistent with previous estimates of the conduction velocity of corticostriate fibres (Buchwald, Price, Vernon & Hull, 1973; Kitai, Kocsis & Wood, 1976; Schultz & Ungerstedt, 1978).

Relative potencies of glutamate and aspartate

A comparison of the excitant potencies of glutamate and aspartate was made on those neurones in the cortex, caudate nucleus and cuneate nucleus which were apparently monosynaptically activated and on a sample of those which were not thus responsive. The comparison was made in two ways, firstly by determining the response amplitude resulting from the application of the same nominal dose (current) of each amino acid, and secondly by determining the dose of aspartate which would produce the same peak response size as a submaximally effective dose of glutamate, usually 80 nA for about 5 s.

The assessment of relative potencies by these means is obviously very approximate. Nevertheless, the relative potencies obtained by the two methods are in close agreement (Table 1).

One of the most interesting aspects of these figures (Table 1) is that there is no significant difference between the potency ratios determined on neurones activated with short latency and those determined on a different population of cells which could not be monosynaptically driven.

α-Aminoadipic acid

The effects of DL-α-aminoadipate (αAA) on amino acid responses were examined on 32 neurones in cerebral cortex, 22 cells in caudate nucleus and 18 in cuneate nucleus. On all the cells studied αAA was able to reduce responses to glutamate and aspartate, but the dose required for this varied considerably. One cell was found whose responses to glutamate and aspartate were completely abolished by 20 nA of αAA applied for 10 s. The most commonly effective dose of αAA to produce an approximately 50% reduction of response size was 40 nA for 30 s. On 15 cells in the caudate nucleus and 21 in cerebral cortex a dose of αAA could be found (about 50 nA for 60 s) which abolished amino acid excitation while reducing acetylcholine excitation by not more than 20% (Figure 1). On 6 of these cells in the cerebral cortex, acetylcholine responses were completely unaffected by these doses of αAA. In the case of 3 caudate and 5 cortical cells, αAA reduced acetylcholine responses roughly in parallel with amino acid responses. On 12 cortical and 8 caudate units, excitation was also induced by applying hydrogen ions from a solution of sodium chloride adjusted to pH 2.0 with 0.1 N HCl. A dose of 80 nA for 30 s usually initiated excitation of cells and only one of these 20 units exhibited a reduction of hydrogen ion excitation at doses of αAA which abolished amino acid responses.

On many cells (26 cortical, 11 caudate and 13 cuneate) αAA showed no evidence of an ability to distinguish between the two amino acids (Figure 2) even when antagonism was achieved gradually using about 20 nA of αAA over 5 min. For the remaining 22 cells (6 cortical, 11 caudate, 5 cuneate) a distinction was apparent, and doses of αAA could be found which completely blocked neuronal responses to

Table 1 A comparison of the relative excitant potencies of glutamate and aspartate on neurones activated by corticofugal axons, and other cells

	*Potency ratio, aspartate:glutamate**		
	Neurones excited monosynaptically	*Other neurones*	*Significance*
Current test	0.76 ± 0.16 (32)	0.83 ± 0.14 (38)	NS
Response test	0.71 ± 0.20 (29)	0.76 ± 0.25 (41)	NS
Significance	NS	NS	

* Mean ± 1 s.d. (*n*). Significance determined by Student's *t* test.

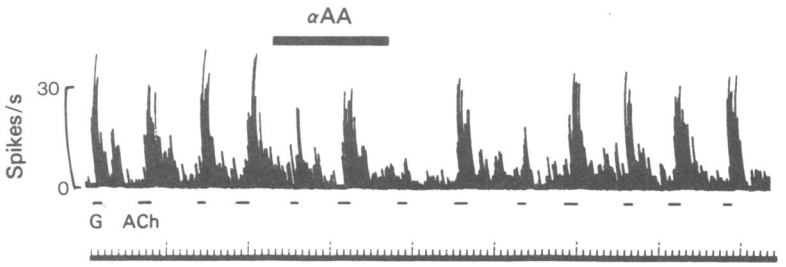

Figure 1 Record of the firing rate of a neurone in the cerebral cortex excited by alternating applications of glutamate, 65 nA (G) and acetylcholine, 80 nA (ACh) by iontophoresis. The application of α-aminoadipate (αAA) with a current of 30 nA selectively reduced the amino acid excitation. Time trace in min and 5 s divisions.

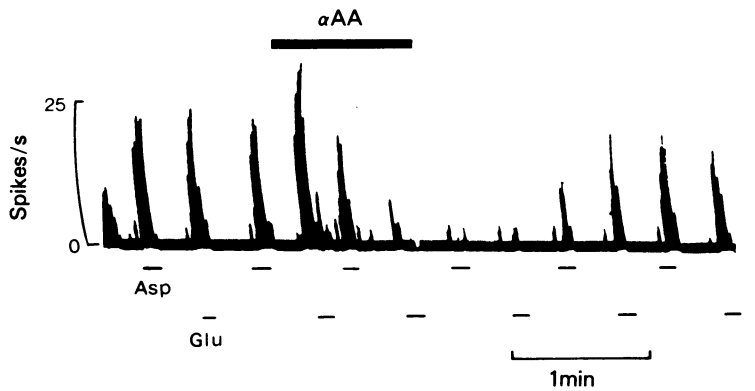

Figure 2 Record of the firing rate of a neurone in the cerebral cortex excited by alternate applications of aspartate, 100 nA (Asp) and glutamate, 60 nA (Glu). The application of α-aminoadipate (αAA) with a current of 30 nA blocked responses to both amino acids on this cell.

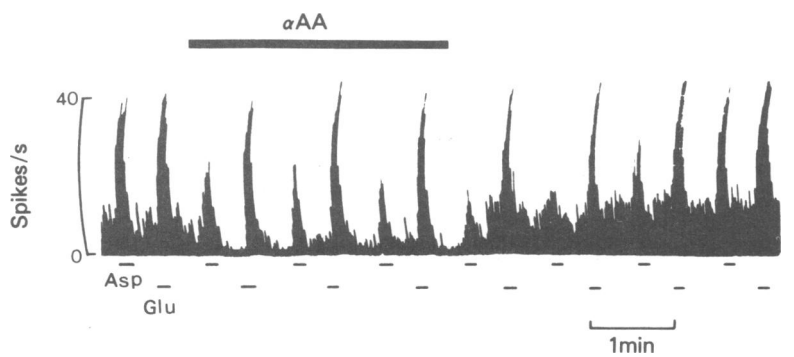

Figure 3 Record of the firing rate of a neurone in the cerebral cortex excited by alternate applications of aspartate, 120 nA (Asp) and glutamate, 100 nA (Glu). The application of α-aminoadipate, 25 nA (αAA) selectively reduced the response to aspartate.

aspartate, while having a lesser effect on glutamate responses (Figure 3). Thus the peak amplitude of glutamate responses were reduced on 12 of these cells, by up to 50% of the original response size, at a time when aspartate responses were totally blocked. Glutamate was unaffected by doses of αAA causing total blockade of aspartate, on 10 units. In all these cases glutamate responses could be reduced in size by increasing the dose of αAA.

α-Aminoadipic acid and synaptic excitation

To investigate the effects of αAA on synaptic responses, stimuli were delivered to the cortical surface

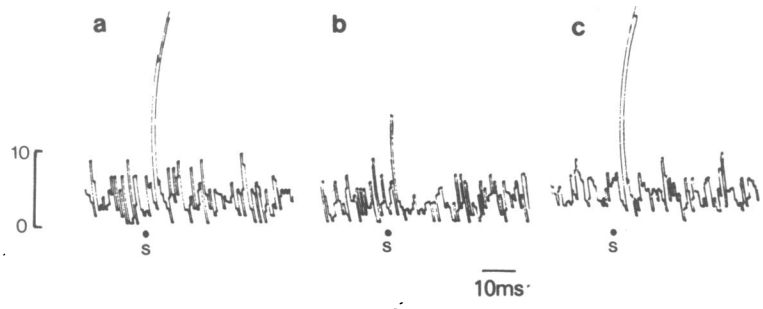

Figure 4 Post-stimulus time histograms of the response of a neurone in the caudate nucleus to stimulation (S) of the cerebral cortex. Each record consists of 64 summated sweeps, using a bin width of 0.5 ms: (a), (b) and (c), before, during and after the iontophoresis of α-aminoadipate (αAA) at a dose of 25 nA for 4 min. Record (b) was started 1.5 min after beginning αAA ejection, and record (c) was begun 2.5 min after ending αAA ejection. The ordinate is events per address; time bar 10 ms.

or pyramidal tracts at 0.5 Hz throughout an examination of the effects of αAA on amino acid responses. The purpose of this protocol was to try and relate any effect of αAA on synaptic excitation to its relative effects on the amino acids.

Thirty-one of the neurones discussed in the previous section yielded results, the number of evoked spikes being reduced during αAA. Thirteen of these cells were in cortex, 5 in caudate and 8 in cuneate. A further 19 cells (10 cortical, 7 caudate and 2 cuneate) showed no change in the synaptically driven activity even after the application of αAA at doses of 100 nA for 10 min.

Of those cells yielding positive results, an example is reproduced in Figure 4. This was a caudate cell on which not only was the total number of evoked spikes reduced, but in particular the initial spike, which was considered to be monosynaptically produced, was abolished. Such an abolition of the early spike was observed on 15 of 24 neurones (6 of 8 cortical, 6 of 10 caudate and 3 of 6 cuneate). The evoked activity recovered roughly in parallel with the recovery of the responses to the exogenous amino acids. This example was typical of most (26) of the 31 neurones in that αAA exhibited no preference for aspartate compared with glutamate (13 cortical, 5 caudate, 8 cuneate). However, 5 cells were encountered in the caudate nucleus in which not only was a clear distinction achieved between the two amino acids, but also acetylcholine was excitatory and could thus act as an independent control. The short latency spikes of these cells were abolished by αAA only at a time when glutamate responses were substantially reduced. If a dose of αAA was used which profoundly reduced aspartate but not glutamate, then the short latency spikes persisted. However, it was noted that the total number of evoked spikes was reduced during the reduction of aspartate. A sequence of histograms illustrating these observations is shown in Figure 5.

Discussion

It is clear that αAA is an effective antagonist of amino acid excitation of central neurones, as described by other groups (Biscoe *et al.*, 1977a, b; McLennan & Hall, 1978). Further, αAA proved to be able to differentiate between responses to aspartate and glutamate on approximately 30% of the cells studied. This property, however, is partly dependent on the brain area considered, as in a study on cerebellar cortex we have found no ability of αAA to distinguish between glutamate and aspartate (Stone, 1979a, b). However, in order to block short latency synaptically evoked excitation, αAA had to be applied in doses which blocked glutamate as well as aspartate. This could be interpreted as favouring a transmitter role for glutamate rather than aspartate in corticofugal axons, but such a reading would be highly dangerous. An equally plausible explanation would be that higher doses of αAA are needed to block synaptically released materials than exogenously applied compounds, doses that also happen to block exogenous glutamate. It may be relevant, however, that at doses of αAA which selectively reduced aspartate excitation, there was a tencency for evoked responses to contain fewer spikes. This may be indicative of a role of aspartate as transmitter from local interneurones as has been suggested in spinal cord (Curtis & Johnston, 1974; Lodge, Headley & Curtis, 1978).

However, it is clear from the present results that αAA can block short-latency synaptically evoked responses at doses which block amino acid excitation but not control responses to acetylcholine or hydrogen ions. This supports previous studies which have indicated the possibility that an amino acid might be released as a neurotransmitter by corticofugal neurones entering the pyramidal tracts (Stone, 1973; 1976) or striatum (Spencer, 1976; Divac *et al.*, 1977). The release of amino acid as a corticofugal transmit-

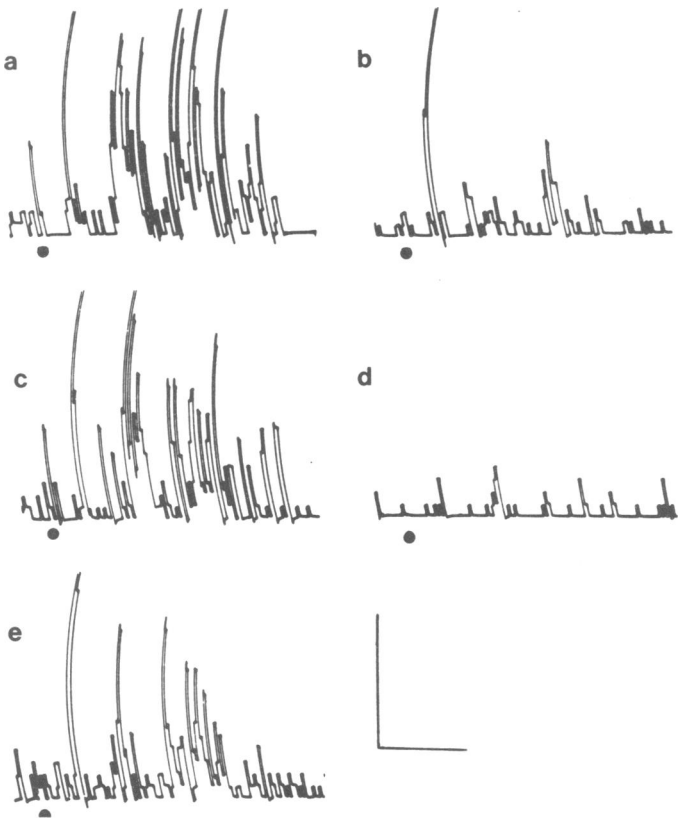

Figure 5 A series of post-stimulus time histograms illustrating the spike activity of a caudate neurone evoked by stimulation of the cerebral cortex. Each histogram consists of 128 superimposed consecutive sweeps using a bin width of 0.5 ms. (a) Control record showing a short latency, probably monosynaptic spike of latency 4.2 ms followed by two polysynaptic spikes at latencies of approx. 11 ms and 18 ms. (b) Record during an application of α-aminoadipate (αAA) 20 nA which abolished responses to iontophoretically applied aspartate while reducing glutamate responses by less than 20% peak size. Note that the polysynaptic spikes were almost completely blocked, while the short latency spike remained. (c) Recovery. Sweeps begun 2 min after (b). (d) Record during an application of αAA, 60 nA, which abolished iontophoretic responses to both glutamate and aspartate. All the evoked spikes were blocked by this application. (e) Recovery. Sweeps begun 2 min after (b). Note that the monosynaptic spike peak is greatly curtailed on this scale in order to show the polysynaptic spikes. The stimulus is indicated by a dot below the record. Calibrations—ordinate scale: 10 counts per bin; abscissa scale: 10 ms.

ter is now sufficiently well documented to merit much fuller investigation both as regards its neurochemistry, and its pharmacology.

A further objective of this study was to compare the relative potencies of glutamate and aspartate in producing excitation of neurones receiving a monosynaptic corticofugal, and therefore probably amino acid releasing innervation with neurones not apparently receiving such an input.

Transport numbers have not been considered in assessing relative potency since we have found that the ejection of amino acids even *in vitro* is highly variable even between ejection periods from a single pipette. We therefore feel that a mean *in vitro* transport number may be misleading if applied to *in vivo* results (see Kelly, 1975). The practice of several other laboratories has therefore been adopted, of using a number of pipettes (usually 2 or 3 per experiment) and sampling both monosynaptically activated and other neurones with each pipette. In this way variations of ejection efficiency with time or between pipettes should not affect the overall pattern of results (Duggan, 1974; McCulloch, Johnston, Game & Curtis, 1974; Biscoe *et al.*, 1976; Hutchinson, McLennan & Wheal, 1978).

As seen from Table 1, glutamate was consistently found to be more potent than aspartate in producing neuronal excitation. Further, there was no demonstr-

able significant difference in the relative potencies of these compounds when tested on the two populations of neurones studied. Clearly, there are sources of error in a study such as this (Duggan, 1974). The assessment of relative potency is not entirely satisfactory, and some neurones not appearing to receive a corticofugal excitation may actually receive such an input not revealed with the stimulating electrode positions used. However, it would seem probable that the excitatory abilities and potencies of glutamate and aspartate are determined by factors other than the mere presence of amino acid releasing synapses. This in turn would suggest that conclusions about transmitter identity based on the relative potency of excitatory amino acids, as has been attempted by several laboratories for synapses in the spinal cord (Duggan, 1974; Biscoe *et al.*, 1976), should be treated with great caution.

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