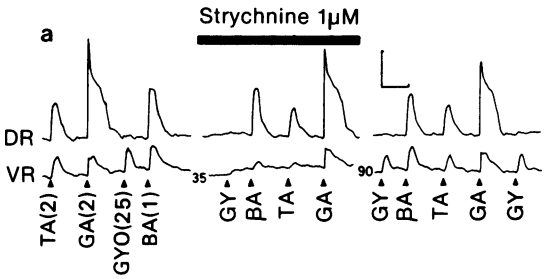

Figure 1a Effect of strychnine on depolarization of motoneurones (VR) and primary afferent terminals (DR) produced by Taurine (TA), GABA (GA), glycine (GY) and β-alanine (βA); concentration (mM) shown. Interval between traces shown in minutes. Calibration 1 mV, 10 minutes.

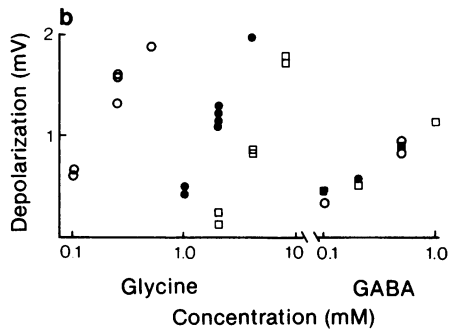

Figure 1b Effect of strychnine 1 μM (●) and 4 μM (□) on responses, measured as in (a) of motoneurones to glycine or GABA (○).

Ringer solution containing procaine 1mM was superfused at 1 ml/minute. Temperature 20°C. Amino acids applied in 2 ml doses.

shown on responses to glycine and GABA. It can be seen that in the case of glycine a parallel shift of the dose-response plot is obtained which allows estimation of the dose ratio for antagonism.

This work was supported by the Medical Research Council.

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Structure-activity studies on an excitatory glutamate receptor of leech neurones

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Glutamate receptors are present on a wide range of animal tissues (Gerschenfeld, 1973; Curtis & Johnston, 1974). There is evidence for more than one type of glutamate receptor, aspartate preferring receptors and glutamate preferring receptors (Morgan, Vrbova & Wolstencroft, 1972; Johnston, Curtis, Davies & McCulloch, 1974). In the present study an attempt is made to determine the preferred form of the excitatory glutamate receptor on leech Retzius cells.

Intracellular recordings were made from Retzius cells from *Hirudo medicinalis* and *Haemopis sanguisauga*. The potentials were amplified using conventional methods and displayed on a Hewlett-Packard pen recorder. The segmental ganglia were removed from the animal and placed in a bath of 20 ml volume. The ganglia were bathed in leech Ringer: NaCl (115); KCl (4); $CaCl_2$ (2); glucose (10); Tris HCl (10); pH 7.4. Drugs were dissolved in leech Ringer and applied over the preparation in a volume of 0.2 ml. The equipotent molar ratio (EPMR) for each analogue was calculated for at least five experiments from the ratio of the number of nmol producing comparable responses. Glutamate was taken as the standard. If the EPMR was greater than one then the compound was less potent than glutamate. The results on *Hirudo* are summarized in Table 1. Similar results were obtained for *Haemopis*.

Since ibotenic acid is approximately equipotent with glutamate and aspartate is less potent this suggests that glutamate may be interacting with the receptor in an extended conformation. Quisqualic acid and kainic acid are also capable of interacting with the receptor in an extended form. The high potencies of these compounds on leech glutamate receptors is of interest and agrees in the case of quisqualic acid with the observations of Shinozaki & Shibuya (1974) on the potency of this compound at the crayfish neuromuscular junction.

We are grateful to Dr H. Shinozaki for a supply of kainic and quisqualic acids and to Professor C.H. Eugster for ibotenic acid.

Table 1 The mean relative potencies ± s.e. mean are given for a series of glutamate analogues and related compounds for their excitatory effects on Retzius cells of *Hirudo medicinalis*. The results are the mean of at least five experiments. The standard dose of glutamate was normally in the range 10–100 nmol. D indicates that the compound is inactive and also desensitizes the receptors to glutamate

Agonist	*Equipotent Molar Ratio (EPMR)*	*± s.e. mean*
L-Glutamic acid	1.1	
D-Glutamic acid	25.5	2.1
(±) 4-Fluoro-glutamic acid	1.13	0.19
DL-α-Methylglutamic acid	1.3	0.14
(±)-β-Methylglutamic acid	D	
(±)-γ-Methylglutamic acid	2.38	0.76
(±)-β-Phenylglutamic acid	> 1000.0	
DL-N-Methylglutamic acid	> 1000.0	
DL-α-Aminoadipic acid	9.3	1.5
DL-α-Aminopimelic acid	D	
L-α-Aminosuberic acid	Inactive	
L-Aspartic acid	11.2	1.7
N-Methyl-DL-aspartic acid	> 1000.0	
DL-Homocysteic acid	0.25	0.04
L-Cysteine sulphuric acid	68.0	13.6
3-Aminopropylphosphonic acid	Inactive	
Quisqualic acid	0.009	0.001
Kainic acid	0.0056	0.001
Ibotenic acid	0.95	0.16

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Specific antagonism of amino acid-induced and dorsal root evoked synaptic excitation of Renshaw cells

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Evidence suggesting that acidic amino acids function as transmitters at excitatory synapses in the mammalian CNS would be considerably strengthened by the discovery of specific blocking agents for this type of putative transmitter. Agents are required which differentiate not only between amino acid and non-amino acid mediated excitation but, ideally, also between excitation mediated by L-glutamate and L-aspartate. Several agents have recently been discovered which, in addition to depressing synaptic activity, specifically block the actions of N-methyl-D-aspartate (NMDA) without reducing responses to kainate (Biscoe, Davies, Dray, Evans, Francis, Martin & Watkins, 1977). These two potent amino acid excitants have been suggested to act as selective agonists for L-aspartate and L-glutamate receptors, respectively (Johnston, Curtis, Davies & McCulloch, 1974). The NMDA-blocking agents, which include HA-966, α,ε-diaminopimelic acid (DAPA), D-α-aminoadipate (D-AA) and Mg^{2+} also depress L-aspartate-induced responses more than L-glutamate-induced responses, while exerting little or no effect on depolarizing responses to Substance P, carbachol or noradrenaline in isolated tissues. However, both HA-966 (Curtis, Johnston, Game & McCulloch, 1973) and Mg^{2+} (Davies & Watkins, 1977) depress ACh-induced ex-