ylated to form methionine, in order for methionine also to be available for other methylations and for protein synthesis.

Though single L-dopa doses did not affect hepatic SAM, the last of ten daily doses, or repeated L-dopa injections at 45-min intervals, caused a significant decline in hepatic SAM. This decline cannot be ascribed to inadequate methionine-activating enzyme levels or to a uniquely great demand for methyl groups, inasmuch as the dose which ultimately depletes (i.e. the last 100 mg/kg injected) has no effect when given singly. We did not measure hepatic methionine levels; however, neither serum nor brain methionine was depressed after the chronic daily administration of L-dopa. The possibility that ATP concentrations can limit hepatic SAM synthesis is suggested by evidence that hepatic ATP concentrations fall when SAM synthesis is stimulated (i.e. by methionine administration).[10]

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Convulsions induced in 10-day-old rats by intraperitional injection of monosodium glutamate and related excitant amino acids

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THERE HAS been considerable controversy concerning the safety of monosodium glutamate as a food additive, due largely to the findings of degenerative lesions in the retina and hypothalamus of infant mice following subcutaneous injection of this acidic amino acid salt.[1] L-Glutamate, like many other acidic amino acids, directly excites mammalian central neurones when applied by microelectrophoresis.[2] The acidic amino acid, *β-N*-oxalyl-L-α,*β*-diaminopropionic acid (ODAP), is a more powerful excitant of central neurones than is L-glutamate;[3] ODAP occurs in the seeds of *Lathyrus sativus* and has been implicated as the agent responsible for the crippling disease, neurolathyrism, which sometimes results from the consumption of these seeds.[4] Several excitant amino acids, including

L-glutamate and ODAP, produce convulsions on suitable injection into mammals, providing that the blood–brain barrier is relatively inefficient as in immature or acidotic animals,[5] or by-passed by the route of administration.[3,6,7] In the present investigation a comparison was made of the convulsant activity of L-glutamate, ODAP and other known excitant amino acids in 10-day-old rats following intraperitoneal injection.

The amino acids were administered to unanaesthetized 10-day-old rats (*Rattus norvegicus*), weighing between 16 and 23 g, by intraperitoneal injection of neutral aqueous solutions (up to 1 M, neutralized where necessary with sodium hydroxide). Adult rats (13-weeks-old, 180–200 g) were similarly injected. The highest dose used was 20 mmoles/kg body wt. Control injections of sodium chloride solutions of the appropriate molarity were used. *N*-Methyl-D- and L-aspartate were prepared by Dr. J. C. Watkins.[8] *β*-*N*-Oxalyl-L-*α*,*β*-diaminopropionic acid and *N*-oxalyl-*β*-alanine were gifts from the late Prof. P. S. Sarma (Bangalore), and ibotenic acid was a gift from Prof. C. H. Eugster (Zürich). The other amino acids were purchased from commercial suppliers.

All of the excitant amino acids tested produced convulsions in the 10-day-old rats, as listed in Table 1. These convulsions were characterized by repeated tonic seizures, involving all limbs, head and tail, and which were of several minutes duration. The time of onset of these seizures was dose-dependent, and was used to compare the relative potencies of these excitant amino acids.

ODAP was comparable with DL-homocysteate as a convulsant, and weaker than *N*-methyl-D-aspartate and ibotenate, at doses of 1 mmole/kg of these amino acids. L-Aspartate, D- and L-glutamate

TABLE 1. CONVULSIONS INDUCED IN 10-DAY-OLD RATS BY INTRAPERITONEAL INJECTION OF AMINO ACIDS

Amino acid	Dose (mmoles/kg)	Time of onset of convulsions (min)
(a) Amino acids known to directly excite central neurones:		
N-Methyl-D-aspartate	0·5	9·3 ± 0·7
N-Methyl-D-aspartate	1	4·8 ± 0·9
Ibotenate	1	7·8 ± 0·5
β-*N*-Oxalyl-L-*α*,*β*-diaminopropionate	1	13·5 ± 1·8
β-*N*-Oxalyl-L-*α*,*β*-diaminopropionate	2	4·5 ± 1·2
DL-Homocysteate	0·5	34·2 ± 3·0
DL-Homocysteate	1	14·3 ± 0·7
DL-Homocysteate	2	5·0 ± 0·9
DL-Homocysteate	5	3·7 ± 0·1
DL-Homocysteate	10	3·8 ± 0·7
DL-Homocysteate	20	3·3 ± 0·6
N-Methyl-L-aspartate	1	18·3 ± 0·6
L-Glutamate	10	*
L-Glutamate	20	30·1 ± 8·6
D-Glutamate	10	*
D-Glutamate	20	33·3 ± 1·5
L-Aspartate	10	*
L-Aspartate	20	36·3 ± 7·6
(b) Amino acids known to directly depress central neurones:		
γ-Aminobutyric acid	20	†
Glycine	20	†
DL-C-Allylglycine	2	57·5 ± 5·4
(c) Amino acids with no direct action on central neurones:		
DL-Methionine-DL-sulphoximine	2	290 ± 17
N-Oxalyl-*β*-alanine	20	*

Values are means ±S.E. of results from 4 animals. * No apparent effects up to 3 hr after injection, † Generalized depression after ca. 5 min.

were inactive at this dose, these amino acids producing convulsions only after some 30 min at the highest dose tested of 20 mmoles/kg.

As excitants of feline central neurones, ODAP is more potent than DL-homocysteate and only slightly less active than *N*-methyl-D-aspartate, the strongest amino acid excitant yet reported.[3] Ibotenate is comparable with DL-homocysteate in potency,[9] whereas L-aspartate, D- and L-glutamate are weaker excitants.[2] Ibotenate, and the related isoxazole, tricholomate, which is also a neuronal excitant,[10] have flavours twenty times more intense than monosodium glutamate.[11] The possible use of these isoxazoles in food formulation has been discussed.[12] It seems possible that the flavour and taste enhancing properties of these amino acids involves depolarization of peripheral taste receptors, analogous with the depolarization of central neurones by excitant amino acids.

While ODAP is thus somewhat weaker as a convulsant than might be expected from its potency as an excitant of feline neurones, these results are compatible with the view that the convulsant and excitant activities of these acidic amino acids have the same basic mechanism, i.e. the direct depolarization of central neurones. Injection of amino acids (γ-aminobutyric acid and glycine) which have a direct hyperpolarizing action on neurones[13] produced a generalized depression of the activity of the 10-day-old rats.

DL-C-Allylglycine, which is a weak depressant of neuronal firing,[14] produced seizures in the 10-day-old rats which were very similar to those produced by the excitant amino acids, but of longer latency. Both the dose required and the time of onset of these seizures are comparable with those reported for adult rats.[15,16] DL-Methionine-DL-sulphoximine also produced convulsions in the 10-day-old rats similar to those reported in adult rats with respect to dose and time of onset.[17] The convulsant actions of DL-C-allylglycine and DL-methionine-DL-sulphoximine have been related to inhibition of glutamate-metabolizing enzymes in adult animals.[17–19] In the 10-day-old rats, some of the excitant amino acids appeared to be more powerful convulsants than DL-C-allylglycine and DL-methionine-DL-sulphoximine, but none of the excitant amino acids produced convulsions in the adult rats used in the present experiments. The adult rats also appeared to be unaffected by injections of γ-aminobutyric acid and glycine. These observations may be interpreted on the basis of blood–brain barrier(s) protecting the adult animals from certain amino acids in the blood stream, or on the basis of other factors such as the levels of pyridoxal 5′-phosphate and the activity of various metabolizing enzymes[20] and transport systems.

A number of excitant amino acids in addition to L-glutamate are now known to produce neuronal damage in the hypothalamus of infant mice following subcutaneous injection.[21] Olney and his colleagues[21] have pointed out that "the close correspondance in molecular specificity associated with neurotoxic and neuroexcitatory properties of simple amino acids suggest the two phenomena may be governed by similar mechanisms of action". The present study indicates that the neuroexcitatory properties are also directly related to the ability of these amino acids to produce convulsions in 10-day-old rats. It is suggested that any excitant amino acid should be suspect as a food additive.

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