Glutamic Acid: Advances in Biochemistry and Physiology, edited by L. J. Filer, Jr., et al. Raven Press, New York © 1979.

Glutamate in the Striatum

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Glutamate, aspartate, and the related amino acids have long been favorite neurotransmitter candidates of the neurophysiologists because of their clear-cut excitatory properties. They have, however, been the despair of neurochemists because their multiple roles in the central nervous system have made it difficult to identify chemically a neurotransmitter pool, if such exists. Glutamic acid, in particular, is incorporated into proteins and peptides, is involved in fatty acid synthesis, contributes (along with glutamine) to the regulation of ammonia levels and the control of osmotic or anionic balance, serves as a precursor for GABA and for various Krebs cycle intermediates, and is incorporated as a constituent of at least two important cofactors (glutathione and folic acid). In view of these many roles, it is not surprising that L-glutamic acid should be the most plentiful amino acid in the adult CNS and show a fairly even distribution.

The excitatory effects of glutamate and aspartate on cerebral cortical cells were first demonstrated more than a quarter of a century ago, but it is only very recently that convincing evidence has been accumulated defining a few glutamergic and/or aspartergic tracts. The high concentrations of glutamate and aspartate in most areas of brain, however, suggest, in conjunction with their physiological properties, that they may be the common excitatory neurotransmitters of the brain just as GABA seems to be the common inhibitory neurotransmitter.

In this chapter, we will describe the apparent neuronal roles of glutamate in the neostriatum and mention, in particular, its possible importance in the etiology of Huntington's chorea.

NEURONAL LOCALIZATIONS OF GLUTAMATE IN THE NEOSTRIATUM

In Glutamergic Neurons

Chemical identification of glutamergic neurons has been difficult because of the lack of a specific chemical index of the neurotransmitter pool. The demonstration of a specific, high affinity, sodium-dependent uptake system for glutamate and aspartate in nerve endings (28) represented a major advance. Although separate uptake

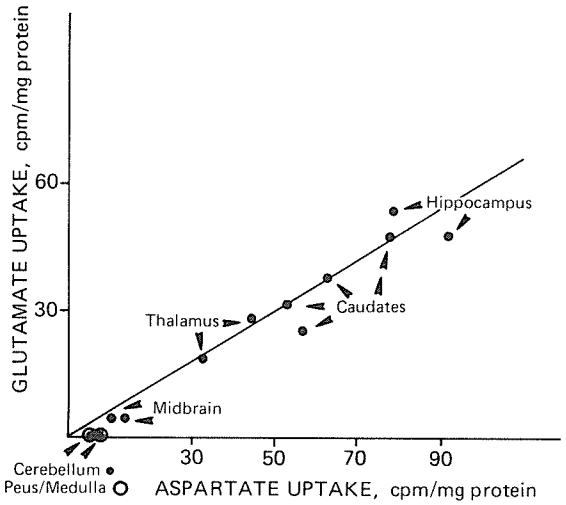

FIG. 1. Correlation between aspartate and glutamate uptakes in various samples of rat brain tissue.

systems for the two amino acids have not yet been distinguished (Fig. 1) and there appears to be high-affinity uptake of glutamate into glial cells as well as into synaptosomes (1,27), it does provide a tool, when combined with selective lesions, for the tentative identification of neurons using these amino acids. These techniques have been used, for example, to suggest that the corticostriatal, entorhinal cortex-hippocampal, retinotectal, primary sensory afferent, and cerebellar granule cell pathways are glutamergic.

Spencer (26) initially suggested that the massive corticostriatal tract might be glutamergic in nature; this suggestion was based on antagonism by diethyl glutamate of the excitation of striatal cells following cortical stimulation. Subsequently, McGeer et al. (22) and Divac et al. (6) found a drop of 40 to 50% in high affinity of glutamate uptake into the synaptosomal fraction of the striatum after ablation or undercutting of the cortex; GABA and dopamine uptake were not affected (Table 1). Both laboratories suggested that the input was glutamergic rather than aspartergic on the basis of the much higher concentration of glutamate as compared with aspartate in the neostriatum, the reported high level of kainic acid (a glutamate analog) binding in the striatum, and Spencer's physiological studies. Subsequently, Kim et al. (15) demonstrated a fall in glutamate levels in the striatum after lesions of the cortex.

It was originally supposed that the thalamostriatal input might also be glutamergic, but large lesions of the thalamus caused no deficit in high-affinity glutamate uptake (Table 1).

Hattori et al. (12) have used axonal transport and autoradiographic methods to define the fine morphology of the probable glutamergic nerve endings in the

TABLE 1. *The accumulation of some putative neurotransmitters and CAT and GAD levels in homogenates of P_2 pellets of caudate-putamen*[a]

	Glutamate (%)	GABA (%)	Dopamine (%)	CAT (%)	GAD (%)
Lobotomized rats	59 ± 4[b]	99 ± 6	110 ± 20	108 ± 8	99 ± 8
Thalectomized rats	105 ± 8	98 ± 4	83 ± 17	100 ± 4	107 ± 3
Lobotomized and thalectomized	58 ± 3[b]	—	—	95 ± 8	95 ± 8

[a] Lesioned side data given as percentage of intact side. CAT, choline acetyltransferase.
[b] $p < 0.001$ for comparison of lesioned and intact sides.

striatum. Figure 2 shows autoradiographs of rat neostriatal terminals labeled by axoplasmic transport following the administration of tritiated proline to the neocortex. The terminals are presumably glutamergic, and all show the same morphology with the common round vesicles and asymmetric contacts typical of Type I excitatory synapses.

The probable importance of this corticostriatal glutamergic tract in the etiology of Huntington's chorea will be discussed later in the section on neurotoxicity of glutamate analogs in the neostriatum.

In GABA-ergic Neurons

The specific localization of glutamic acid decarboxylase (GAD) in GABA-ergic neurons in brain indicates that glutamate is the immediate precursor of this inhibitory neurotransmitter. The brain content of GABA is 200- to 1,000-fold greater than that of neurotransmitters such as dopamine, noradrenaline, acetylcholine, and serotonin. Some of the highest levels of GABA and GAD in brain are found in the basal ganglia, particularly in the globus pallidus and substantia nigra, suggesting a prominent role for this transmitter in the extrapyramidal system. Early uptake studies on radioactive GABA into slices of the caudate-putamen, globus pallidus, and substantia nigra suggested that the uptake was primarily into nerve endings in the substantia nigra, whereas it was into cell bodies as well as nerve endings in the other areas (Table 2) (13).

At least three pathways of the basal ganglia utilize GABA and therefore contain glutamate as a GABA precursor.

Neostriatal interneurons. The probability that much of the GABA in the neostriatum is contained in interneurons is suggested by the small and usually insignificant losses of GABA or GAD following lesions of all known afferents to the neostriatum (20).

Striatonigral pathway. It has been known for many years that a prominent striatonigral path exists with highly preferential innervation of the pars reticulata. More recently, it has been shown that lesions of the neostriatum or hemitransections anterior to the globus pallidus will cause some reduction in nigral GAD (9,14).

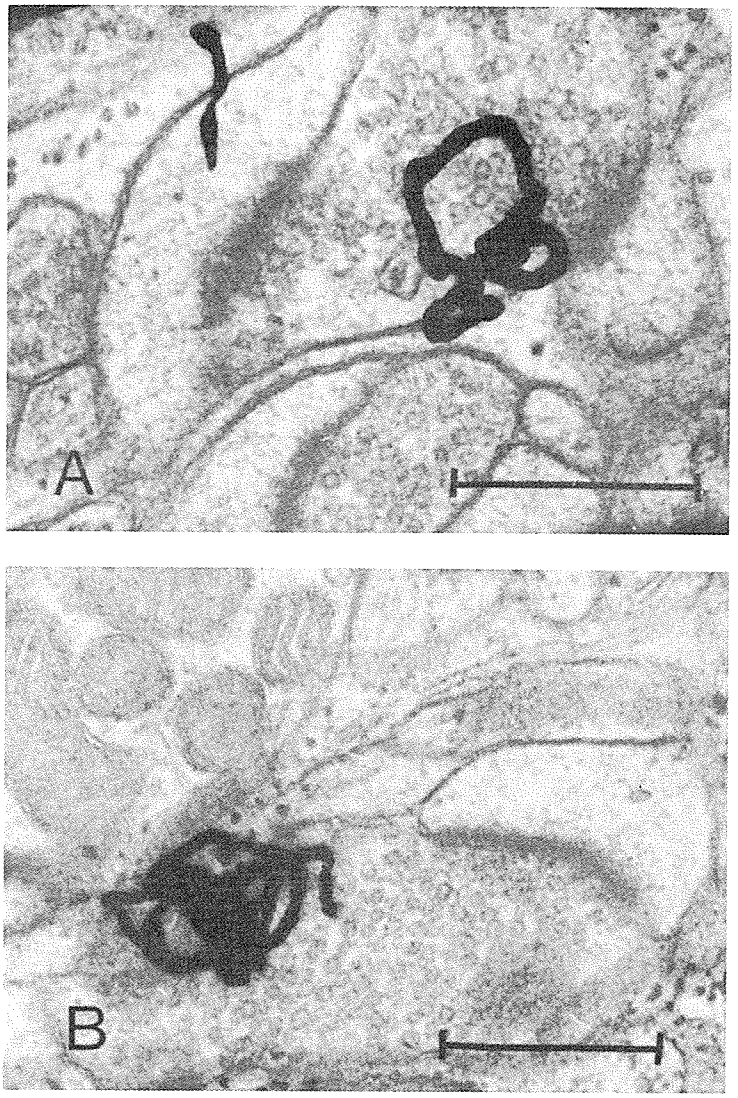

FIG. 2. Two examples of labeled boutons in control rat striatum 7 days after [^{3}H]proline injections into the frontal cortex. Synaptic vesicles are uniformly distributed throughout the bouton. Bars indicate 0.5 μm.

Selective lesions (8,23) suggest that the cell bodies of these reticulata afferents originate in the caudal and lateral aspects of the neostriatum. Since the pathway traverses the globus pallidus, it has been suggested that there may be some terminations within the pallidum itself (8).

Pallidonigral pathway. Compelling evidence in favor of a descending pallidoni-

TABLE 2. *Uptake of [^3H]GABA into slices of various regions of the rat brain*

	Caudate-putamen		Globus pallidus		Substantia nigra	
	% Area	% Grains	% Area	% Grains	% Area	% Grains
Cell soma	47	28	48	42	43	6
Nerve terminal	17	52	15.5	27	18	70
Dendrite	22	15	21	19	24	17
Axon	6.5	2	7.5	6	10.5	4
Glial space and others	7.5	3	8.0	6	4.5	3

From Hattori et al., ref. 13.

gral GABA-containing pathway came originally from studies indicating that electrolytic lesions of the globus pallidus or hemitransections of the brain at the level of the subthalamus led to losses of up to 80% in the GAD activity in the substantia nigra, whereas transections anterior to the globus pallidus led to much smaller losses in GAD (19). The existence of this pathway was established by anterograde axoplasmic flow studies following the injection of ^3H-leucine into the globus pallidus. Comparative studies were done following similar injections into the caudate-putamen (NCP). Protein labeling of the nigra resulted from both these injections, there being preferential transport to the zona compacta following pallidal injections and to the zona reticulata following NCP injections (11).

The existence of the pallidonigral tract has been confirmed by retrograde transport of HRP (3,10) and the findings relative to GAD duplicated by Mroz et al. (23). Axonal transport of radioactive GABA in this tract has also been demonstrated (19).

More recently, additional evidence supporting the existence of both GABA-ergic interneurons of the neostriatum and striatonigral GABA-ergic tracts has come from studies of GABA-ergic indices in extrapyramidal nuclei following striatal injections of kainic acid. This analog of glutamate appears to cause destruction only of neurons with perikarya in the injected area and to spare axons of passage and afferent nerve terminals. The biochemical changes in extrapyramidal nuclei following striatal injections of kainic acid (Table 3) are consistent with this hypothesis of its selectivity of action, when considered in conjunction with the presumed biochemical neuroanatomy of the extrapyramidal system (Fig. 3). In particular, the severe losses of GAD, GABA, and GABA uptake in the neostriatum and the substantia nigra are consistent with destruction of GABA-ergic striatal interneurons and striatonigral neurons. Similarly, the lack of a deleterious effect of kainic acid injections on glutamate uptake in the striatum is consistent with the supposition that such uptake reflects the integrity of the corticostriatal glutamergic path.

NEUROTOXICITY OF GLUTAMATE ANALOGS IN THE NEOSTRIATUM

Initial reports on the biochemical deficits resulting from local injections of kainic acid into the neostriata of rats were of particular interest because the morphological

TABLE 3. *Biochemical changes reported in rats given intrastriatal injections of kainic acid and in Huntington's chorea*

Area and biochemical index	Striatal kainic acid	Huntington's chorea
Neostriatum		
GABA-ergic indices[a]	Decreased markedly	Decreased markedly
Cholinergic indices[a]	Decreased markedly	Decreased markedly
Dopaminergic indices[a]	Normal or elevated	Normal or elevated
Serotonergic indices[a]	Normal	Normal
Noradrenergic indices[a]	Normal	Normal
Angiotension converting enzyme	Decreased markedly	Decreased markedly
Receptors[b] for:		
AcCh (muscarinic)	Decreased markedly	Decreased markedly
Serotonin	Decreased markedly	Decreased markedly
GABA	Increased or decreased	Normal or decreased
Substantia nigra		
GABA-ergic indices[a]	Decreased markedly	Decreased markedly
Substance P levels	Decreased markedly	Decreased markedly
Tyrosine hydroxylase levels	Normal	Normal

[a] Neuronal indices used include activity of the synthetic enzyme and levels, uptake, and release of transmitter.

[b] "Receptor" activity refers to sodium-independent binding in synaptic membrane fractions and does not imply pre- or postsynaptic localization or physiological activity.

From Coyle et al., ref. 4.

and biochemical changes were very similar to those reported for Huntington's chorea. Further studies on the biochemical pathology of persons dying with Huntington's chorea and of rats injected intrastriatally with kainic acid have produced additional support for the use of this preparation as an animal "model" of Huntington's chorea (Table 3). Psychopharmacological data so far reported also support the analogy (7).

The fact that kainic acid is recognized as an analog of glutamate, and that glutamate and aspartate, as well as other excitatory amino acids, also have neurotoxic properties, has led to the supposition that Huntington's chorea and other human diseases involving general neuronal loss in specific brain loci may involve glutamate and/or aspartate neuronal systems in their etiology. In particular, it has been suggested that the neostriatal cell death in chorea may be due to chronic functional overactivity of the corticostriatal glutamergic tract. Several possibilities that could have a genetic basis might be considered. For example, there may be enhanced release of glutamate or impaired reuptake of intrasynaptic glutamate causing excessive stimulation of excitatory receptors and ultimately neuronal death. Alternatively, supersensitivity of excitatory receptors or some more general membrane or metabolic disturbance that becomes manifest in cells undergoing glutamate-induced depolarization could be operative. Although these mechanisms are purely speculative, they do suggest new directions for research in the causes of such neuronal degeneration as occurs not only in Huntington's disease, but in senile

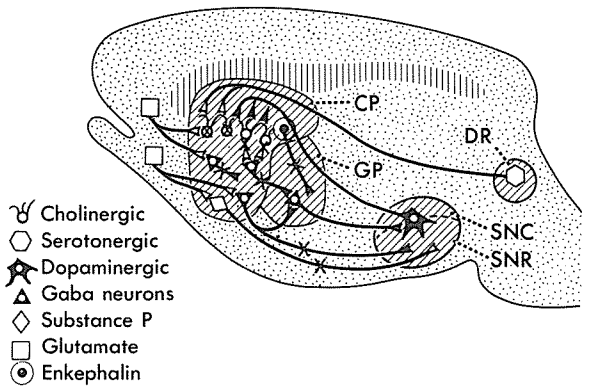

FIG. 3. Hypothesized biochemical neuroanatomy of extrapyramidal system with × indicating neurons affected by intrastriatal injections of kainic acid. Hypothesized encephalin path based on evidence of Cuello and Paxions (5); evidence for other tracts has been recently reviewed (21). CP, caudate-putamen; GP, globus pallidus; DR, dorsal raphe; SNC and SNR, zona compacta and zona reticulata of the substantia nigra.

dementia and some of the ataxias. It is clear that any information shedding more light on the mechanism of kainic acid-induced toxicity is of great importance to a study of this hypothesis, as well as to the application of kainic acid and its analogs as selective lesioning tools in neurobiology.

Olney et al. (24) initially suggested that the toxic actions of glutamate and its analogs, including kainic acid, were through their excitatory action at the glutamate receptor, i.e., in excess, these compounds excite the cells to death (Fig. 6a). According to the theory, no particular toxic action of the administered agent would be necessary beyond persistently activating excitatory receptors: damage would be consequent to ionic shifts exceeding the capacity of membrane pumps to restore and maintain the normal resting potential gradient between the inside and the outside of the cells. Thus, the level of sodium ions would become persistently high inside the cell, whereas potassium ions would leak to the outside. Other ionic changes would also occur, shifting the intracellular ionic balance to a state incompatible with the continued existence of the neuron.

Morphological data from our laboratory (12) offer some support for the hypothesis that glutamergic receptor sites in the striatum are particularly sensitive to the toxic effects of kainic acid. In double labeling experiments, ^{3}H-proline was injected into the frontal cortex of rats, and 7 days later, 1.25 nmoles of kainic acid were injected into the ipsilateral striatum. The animals were sacrificed 10 hr after the kainic acid injection and the control and kainic acid-injected striata examined by light and electron microscopy. In both striata, boutons were the only tissue compartment that was specifically labeled by the radioactive proteins axonally transported from the frontal cortex. Eighty percent of the labeled terminal boutons in the kainic acid-injected neostriata made asymmetrical synaptic contacts with degenerating dendritic spines, and the relative grain density in such boutons was 3.25 times

TABLE 4. *Distribution of silver grains in terminal and preterminal boutons of the kainic acid-affected striatum 7 days after [^{3}H]-proline injection into the ipsilateral frontal cortex*[a]

	% Total grains in boutons	% Total area of boutons	Relative grain density (% grain/% area)
Asymmetric terminal boutons			
On normal dendrites	7	19	0.4
On degenerating dendrites	42	33	1.3
Symmetrical boutons (all on normal dendrites)	3	10	0.3
Preterminal boutons	48	38	1.3

[a] A total of 88 grains was counted in boutons.

greater than that in boutons in synaptic contact with normal dendritic elements (Table 4). In the control striata the boutons showed the uniform distribution of synaptic vesicles evident in Figure 2; in the kainic acid-injected striata, on the other hand, the labeled boutons showed clusters of vesicles that were sometimes, but not always, close to the presynaptic membrane. There was invariably considerable empty space in each such labeled bouton (Fig. 4). The preferential labeling of boutons in contact with degenerating dendritic elements supports the view that neuronal elements carrying many glutamate receptors may be particularly sensitive to the toxic effects of kainic acid (12).

Our experiments on the striatum, however, have led us to propose that kainic acid does not itself act directly on the glutamate receptor since injections of kainic acid do not appear to have much neurotoxic action in the striatum after degeneration of the corticostriatal glutamergic tract (Table 5) (18).

By contrast, thalamic lesions fail to alter the kainic acid-induced neurotoxicity. This indicates that the protection observed after cortical lesions is not a nonspecific effect. Denervation-induced subsensitivity of glutamate receptors has been suggested as a possible explanation. This seems unlikely, both because denervation commonly induces super- rather than subsensitivity and because the time course of the effect (Fig. 5) is that to be expected if the inhibition of kainic acid-induced neurotoxicity depends on degeneration of the presynaptic neurons.

In an attempt to explain these results we are examining three hypotheses.

Loss of excitatory input. One possible hypothesis suggests that removal of the corticostriatal excitatory input reduces the basal level of activity of the neostriatal cells to a point where the additional effects of small doses of kainic acid are no longer able to excite the cells to death. But this simple hypothesis does not explain why lesions of the thalamic input, which is also excitatory, should fail to provide protection. Kainic acid, however, may act selectively on glutamate-receptive neurons to potentiate the action of glutamate. Such potentiation of glutamate-induced excitation, with little or no direct excitatory action of its own, has been reported for kainic acid at the crayfish neuromuscular junction (25).

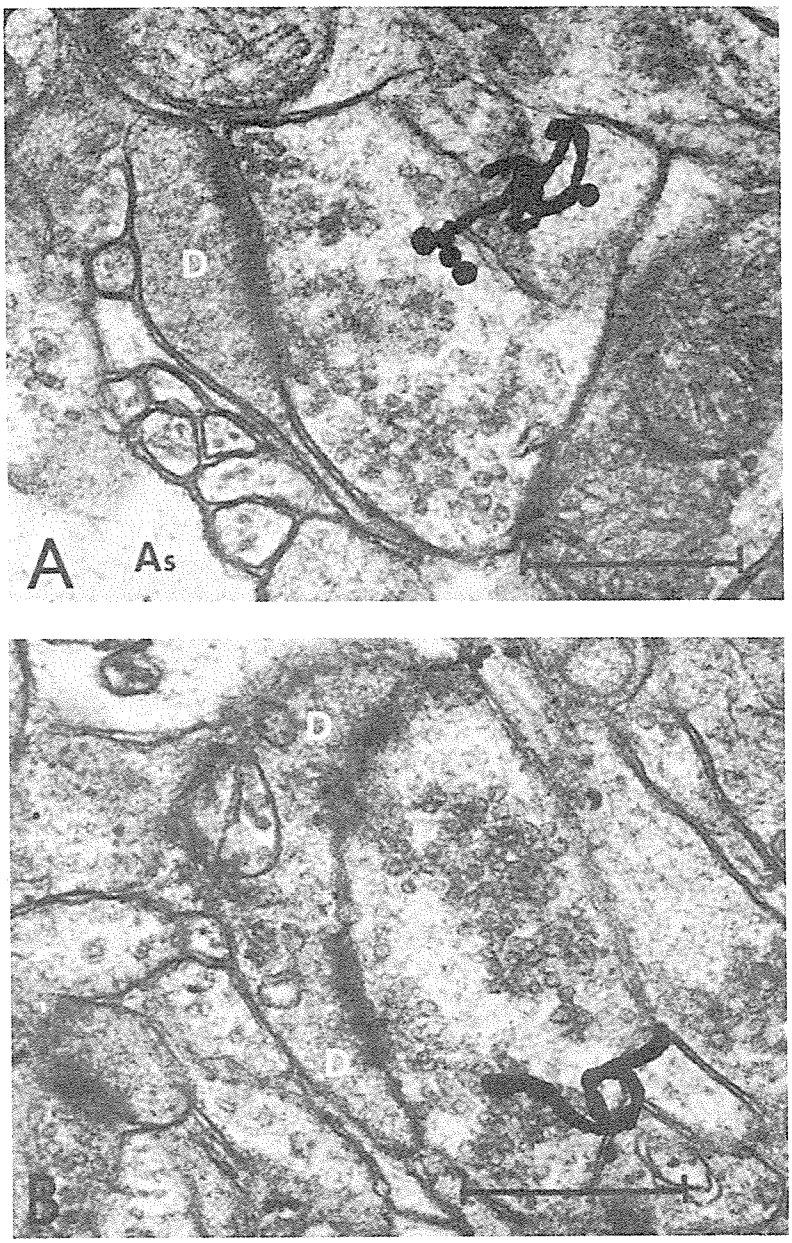

FIG. 4. Two examples of labeled boutons in the kainic acid-affected striatum. Synaptic vesicles form clusters that often appear close to the presynaptic membrane. **As:** astrocyte; **D:** degenerating dendritic spine. Bars indicate 0.5 μm.

TABLE 5. *Protein and enzyme levels in neostriata injected with 2.5 nmoles of kainate as a percentage of those on the contralateral side*

	Protein	GAD	CAT
Unlesioned	92.8 ± 3.6	40.0 ± 0.7	43.8 ± 2.5
Corticostriatal tract lesion	93.4 ± 1.9	95.7 ± 6.3[a]	86.5 ± 5.3[a]
Thalamic lesion	91.4 ± 5.0	40.7 ± 7.8	45.1 ± 8.9

The absolute levels for the contralateral side were comparable in all groups with those found in rats not subjected to any manipulation. Control values were protein, 114.2 ± 3.8 mg/g tissue; GAD, 14.68 ± 0.38 μmoles/hr/100 mg protein; CAT, 34.08 ± 0.81 μmoles/hr/100 mg protein. Six rats per group. All values mean ± SE.

[a] $p < 0.001$ for comparison with data from unlesioned rats.

Release of glutamate or inhibition of its uptake. According to this hypothesis, kainic acid may not act directly, as supposed in Fig. 6a, on the postsynaptic glutamate receptors, but may cause release of glutamate and/or inhibit its reuptake into glutamate nerve endings or glia (Fig. 6b). Either way, the neurotoxicity of

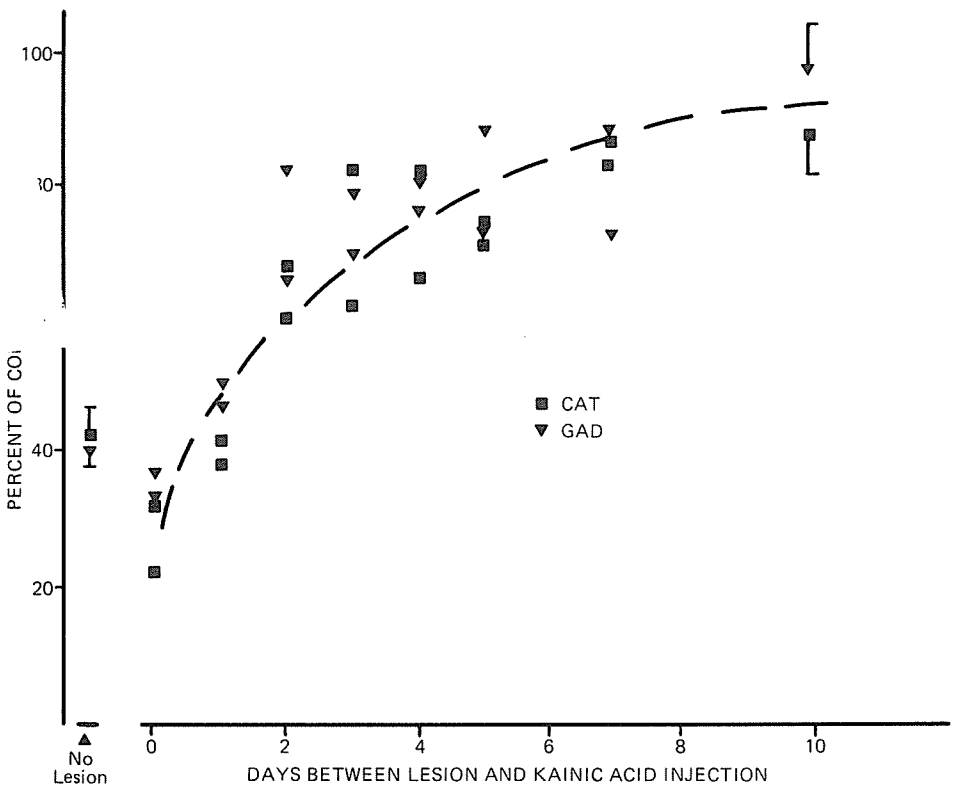

FIG. 5. CAT and GAD activities (as a percentage of control) in the striata of rats injected with 3 nmoles kainic acid at various times after lesions of the corticostriatal tract.

kainic acid would be indirect and due to abnormally high levels of glutamate in the synaptic cleft.

It can be argued that this hypothesis is not tenable because of the very large amounts of glutamate that are required to produce neuronal damage on direct injection into the striatum. However, such exogenous glutamate may well be taken up quickly into glial cells or other compartments so that high concentrations are unable to reach the glutamate receptors.

This hypothesis assumes that kainic acid behaves in glutamate systems much the same way as amphetamine behaves in catecholamine systems. Lakshmanan and Padmanaban (16,17) have previously suggested that the convulsive effects of kainic acid, N-methyl-D-aspartic acid, and β-N-oxalyl-L-α,β-dimethylpropionic acid (ODAP), as well as the neurotoxicity of ODAP (16), might be mediated by glutamate. In support of this hypothesis both they and ourselves have found that kainic acid inhibits the high-affinity, sodium-dependent accumulation of glutamate

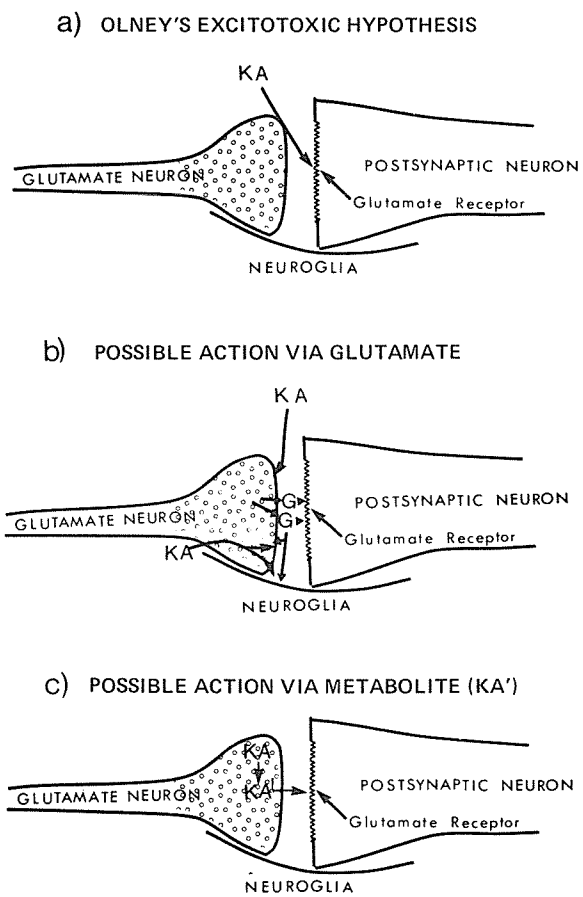

FIG. 6. Various hypothesized mechanisms for the neurotoxic action of kainic acid.

by synaptosomal preparations (Table 6). The effective concentrations are high, but comparable to those which might well occur during intrastriatal injections of this neurotoxin. Similar results are obtained in a calcium-free medium, suggesting kainic acid-induced release may not be involved. Preliminary evidence also suggests that kainic acid does not displace sodium-independent glutamate binding to synaptic membrane preparations of the neostriatum, although glutamate displaces kainic acid binding. Both of these results would be in accord with the hypothesized mechanism shown in Figure 6b.

Metabolite hypothesis. The metabolism of kainic acid in brain tissue has not yet been worked out. It is quite possible that some material formed from kainic acid could be the toxic agent. If this is the case, it seems necessary, in view of the protective effects of the corticostriatal lesion, to postulate that the metabolism of kainic acid producing the toxic material occurs in the glutamergic nerve endings (Fig. 6c). There is little or no evidence to support this hypothesis, but it seems worth further exploration, as do all avenues of research that might lead to an understanding of the mechanism of the neurotoxicity induced by excitatory amino acids.

GLUTAMINASE IN THE STRIATUM

The probable localization of much of the glutaminase activity of brain in the synaptosomal fraction (2) suggests that it might play an important role in the maintenance of the transmitter pool of glutamate, as well as in the formation in GABA-ergic nerve endings of glutamate to be used as a precursor of GABA. The data indicating that the glutamergic and GABA-ergic systems of the neostriatum can be selectively affected by lesions of the corticostriatal tract or by intrastriatal kainic acid injections suggested that this system might be used to explore the relative

TABLE 6. *Effect of kainic acid on sodium-dependent accumulation of [^{14}C]glutamate, [^{14}C]GABA, or [^{3}H]dopamine by synaptosomal fraction of rat neostriatal homogenates*

	% Uptake[a]		
Concentration of kainate (M)	Glutamate accumulation	GABA accumulation	Dopamine accumulation
10^{-3}	24 ± 2	92 ± 9	109 ± 11
3.16×10^{-4}	61 ± 2	112 ± 8	104 ± 6
10^{-4}	74 ± 4	119 ± 10	114 ± 10
3.16×10^{-5}	79 ± 9	102 ± 7	107 ± 8
10^{-5}	94 ± 5		
10^{-6}	93 ± 7		

All accumulation studies were done as previously described (22) on the P_2 fraction of rat neostriatal homogenates using 10^{-6} M of the radioactive material; the kainate solution was made up immediately before use and was present during the 5-min preincubation and the 5-min exposure to radioactive material. Control accumulations (in μmoles/5 min/g protein) were 1.67 ± 0.12, glutamate; 1.34 ± 0.09, GABA; and 0.11 ± 0.04, dopamine.

[a] As a percentage of that observed with the same homogenates in the absence of kainate.

amounts of glutaminase associated with these two neuronal types. Glutaminase activity in the neostriatum was therefore measured in rats that had received intrastriatal injections of kainic acid or lesions of the corticostriatal tract at least 10 days before sacrifice.

Figure 7 illustrates typical results on the animals injected with varying amounts of kainic acid. The decrement in glutaminase correlated significantly with the decrement in GAD, and the intercept on the x-axis was such as to suggest that some 60% of the glutaminase activity in the neostriatum is located in GABA-ergic structures (or at least some structures destroyed by the kainic acid injection), whereas 40% is in some unaffected compartment(s). Of the systems so far known to be affected by kainic acid (Table 3), only the GABA-ergic system would appear likely to contain glutaminase. The glutamate uptake in these kainic acid-injected animals was not depressed and indeed, in some, was raised somewhat above the contralateral control striatum. An attempt to take the individual glutamate uptakes into account by calculating for the data a line of correlation of the form

$$\text{glutaminase activity} = a + b\ (\text{GAD activity}) + c\ (\text{glutamate uptake})$$

was unsuccessful; the coefficient of correlation was much lower than for the line of regression shown in Fig. 7.

On the other hand, in animals with lesions of the corticostriatal tract, we could

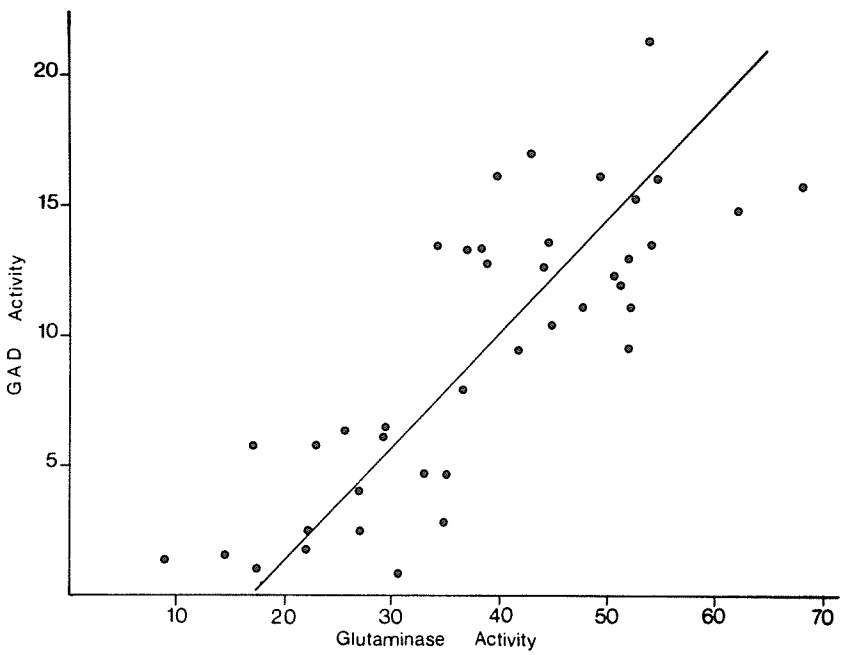

FIG. 7. Correlation between glutaminase and GAD activities (in μmoles/hr/100 mg protein) in the neostriata of rats sacrificed 10 days after injection of 0 to 10 μmoles kainic acid.

not demonstrate a significant correlation between glutaminase activity in the neostriatum and glutamate uptake in that structure. In these animals, GAD activity was not significantly affected by the lesion. These results were disappointing since we had hoped that glutaminase activity might be a convenient index, used alone or together with measurements of GAD, for the integrity of glutamergic systems. These data, however, offer no support for the supposition that the neurotransmitter pool of glutamate may be derived directly from glutamine in the glutamergic nerve endings.

Experiments on the subcellular localization of glutaminase in control rat neostriata indicated that approximately 60% was in the P_2 synaptosomal fraction. This figure is higher than previously reported from other brain areas (2), but is consistent with the results from kainic acid-injected rats. Taken together, these data suggest that about 40% of the glutaminase in the neostriatum is associated with glia and about 60% with GABA-ergic systems.

CONCLUSION

Glutamate certainly plays important multiple roles in the neostriatum, as it probably does in most regions of brain. It remains a challenge to neuroscientists to develop and apply techniques capable of sorting out its complex functions. The very real possibility that glutamergic systems may play a key role in the mechanisms underlying neuronal losses such as occur in Huntington's chorea, senile dementia, and ataxias emphasizes the importance of concentrated research in this field.

ACKNOWLEDGMENTS

This work was supported by the Huntington's Chorea Foundation, Inc., the W. Garfield Weston Foundation, and the Medical Research Council of Canada.

REFERENCES

1. Balcar, V. J., and Johnston, G. A. R. (1977): *J. Neurochem.*, 20:529–539.
2. Bradford, H. F., and Ward, H. K. (1976): *Brain Res.*, 110:115–125.
3. Bunney, B. S., and Aghajanian, G. K. (1976): *Brain Res.*, 117:423–435.
4. Coyle, J. T., McGeer, E. G., McGeer, P. L., and Schwarcz, R. (1978): Neostriatal injections: A model for Huntington's chorea. In: *Kainic Acid,* edited by E. G. McGeer, J. W. Olney, and P. L. McGeer, pp. 123–138. Raven Press, New York.
5. Cuello, A. C., and Paxinos, G. (1978): *Nature,* 271:178–180.
6. Divac, I., Fonnum, F., and Storm-Mathisen, J. (1977): *Nature,* 266:377–378.
7. Fibiger, H. C. (1978): Kainic acid lesions of the striatum: A pharmacological and behavioral model of Huntington's disease. In: *Kainic Acid,* edited by E. G. McGeer, J. W. Olney, and P. L. McGeer pp. 161–236. Raven Press, New York.
8. Fonnum, F., Gottesfeld, Z., and Grofova, I. (1978): *Brain Res.*, 143:125–138.
9. Fonnum, F., Grofova, I., Rinvik, E., Storm-Mathison, J., and Waldberg, F. (1974): *Brain Res.*, 71:77–92.
10. Grofova, I. (1975): *Brain Res.*, 91:286–291.
11. Hattori, T., Fibiger, H. C., and McGeer, P. L. (1975): *J. Comp. Neurol.*, 162:487–504.
12. Hattori, T., McGeer, E. G., and McGeer, P. L. (1977). *Neurosci. Abstr.*, 7:38.

13. Hattori, T., McGeer, P. L., Fibiger, H. C., and McGeer, E. G. (1973): *Brain Res.*, 54:103–114.
14. Kim, J. S., Bak, I. J., Hassler, R., and Okada, Y. (1971): *Exp. Brain Res.*, 14:95–104.
15. Kim, J. S., Hassler, R., Haug, P., and Paik, K. S. (1977): *Brain Res.*, 132:370–374.
16. Lakshmanan, J., and Padmanaban, G. (1974): *Nature*, 249:469–471.
17. Lakshmanan, J., and Padmanaban, G. (1974): *Biochem. Biophys. Res. Commun.*, 58:690–698.
18. McGeer, E. G., McGeer, P. L., and Singh, K. (1978): *Brain Res.*, 139:381–383.
19. McGeer, P. L., Fibiger, H. C., Maler, L., Hattori, T., and McGeer, E. G. (1974): Evidence for descending pallido-nigral GABA-containing neurons. In: *Advances in Neurology*, Vol. 5, edited by F. H. McDowell and A. Barbeau, pp. 153–160. Raven Press, New York.
20. McGeer, P. L., and McGeer, E. G. (1975): *Brain Res.*, 91:331–335.
21. McGeer, P. L., and McGeer, E. G., and Hattori, T. (1979): Transmitters in the basal ganglia. In: *Amino Acids as Chemical Transmitters*, edited by F. Fonnum, pp. 123–142. Raven Press, New York.
22. McGeer, P. L., McGeer, E. G., Scherer, U., and Singh, K. (1977): *Brain Res.*, 128:369–373.
23. Mroz, E. A., Brownstein, M. J., and Leeman, S. E. (1977): *Brain Res.*, 125:305–311.
24. Olney, J. W., Sharpe, L. G., and de Gubareff, T. (1975): *Neurosci. Abstr.*, 5:371.
25. Shinozaki, H. (1978): The discovery of novel actions of kainic acid and related compounds. In: *Kainic Acid*, edited by E. G. McGeer, J. W. Olney, and P. L. McGeer, pp. 17–36. Raven Press, New York.
26. Spencer, H. J. (1976): *Brain Res.*, 102:91–101.
27. Stewart, R. M., Martuza, R. L., Baldessarini, R. J., and Komblith, P. L. (1976): *Brain Res.*, 118:441–452.
28. Wolfsey, A. R., Kuhar, M. J., and Snyder, S. H. (1971): *Proc. Natl. Acad. Sci. USA*, 68:1102–1106.