Axon-Sparing Brain Lesioning Technique

Simson *et al.* (*1*) claim to have developed a technique for inflicting brain lesions that spares nerve fibers. In view of the importance of a solution to the "fiber of passage problem," certain features of this report require comment. First, Simson *et al.* neglected to cite a number of studies on the central excitatory and neurotoxic effects of glutamate and its analogs that followed Olney's early studies of monosodium glutamate in the hypothalamus (*2–4*). In three of these studies the compound was injected intracerebrally outside the hypothalamus, and all the studies contained evidence directly relevant to the fiber of passage problem. In the context of these studies, the report of Simson *et al.* adds strength to the case for glutamate analogs as fiber-sparing lesion agents [see (*3*), and discussion in (*5*)], but the evidence provided does not by itself establish the claim of the authors.

The claim for a generally applicable lesion method requires evidence for the effectiveness of the compound in more than a single brain locus. In the case of glutamate analogs, and particularly kainic acid, the literature cited (*2–4*) does provide evidence that their effects are not limited to the hypothalamus. At the same time, however, the most recent studies tend to indicate differential susceptibilities of different neuronal populations to this type of compound (*6–9*).

The Simson *et al.* report also does not provide convincing evidence for the functional integrity of spared fibers. What percentage of passing fibers must be spared to prevent hypothalamic hyperphagia? How much intermittent conduction block and decreased conduction velocity is compatible with an absence of drastic effects on an animal's body weight? How is the myelin sheath affected by the treatment? Such factors are of crucial importance to the functional role of many, if not most, fiber systems. One would like to see tests for the functional integrity of fast conducting, myelinated fibers passing through a region of neuronal necrosis. A convincing test would be one in which the loss of neuronal perikarya on the one hand, and the loss of functional integrity of fibers on the other, were associated with clearly distinguishable and separate changes in phasic behavioral responses. It is to be hoped that future studies adopt this more rigorous definition of the problem in order to validate the cytological specificity of fiber-sparing lesion agents. Otherwise the "fiber of passage problem" might be replaced by a "degree of sparing problem."

BJÖRN MERKER

Department of Psychology, Massachusetts Institute of Technology, Cambridge 02139

References

1. E. L. Simson, R. M. Gold, L. J. Standish, P. L. Pellett, *Science* **198**, 515 (1977).
2. J. W. Olney, O. L. Ho, V. Rhee, *Exp. Brain Res.* **14**, 61 (1971); J. W. Olney, V. Rhee, O. L. Ho, *Brain Res.* **77**, 507 (1974).
3. J. W. Olney, L. G. Sharpe, T. de Gubareff, *Neurosci. Abstr.* **5**, 371 (1975).
4. J. T. Coyle and R. Schwarcz, *Nature (London)* **263**, 244 (1976); E. G. McGeer and P. L. McGeer, *ibid.*, p. 517.
5. R. Schwarcz and J. T. Coyle, *Brain Res.* **127**, 235 (1977).
6. G. Di Chiara, M. Olianas, M. Del Fiacco, P. F. Spano, A. Tagliamonte, *Nature (London)* **268**, 743 (1977).
7. R. M. Herndon and J. T. Coyle, *Science* **198**, 71 (1977).
8. J. V. Nadler, B. W. Perry, C. W. Cotman, *Nature (London)* **271**, 676 (1978).
9. T. de Gubareff and J. W. Olney, *Neurosci. Abstr.* **7**, 515 (1977).

8 December 1977; revised 3 March 1978

We agree with Merker that more data are needed to confirm our monosodium-L-glutamate (MSG) axon-of-passage sparing lesioning technique. Since our report (*1*) was published, we have infused MSG into other brain regions, and in each case found evidence of fiber sparing. These regions include medulla (Weigert-Weil myelin stain) (*2*), caudate nucleus (Weigert-Weil stain and histofluorescence) (*3*), and optic tract (electrophysiology) (*4*). Electrophysiological recordings from the heavily myelinated optic tract show that persistent evoked potentials can be induced by light flashes after the infusion of MSG into the optic tract (*4*). Multiple-unit electrophysiological recordings from a cellular area (paraventricular nucleus) showed a gradual decline in activity starting 1½ hours after the infusion of MSG into the paraventricular nucleus (*4*). By 3 hours after infusion there was virtually no activity in the infused area. These findings support our suggestion that MSG spares fibers of passage, while indicating that it does affect cell bodies.

With regard to the proposal that kainic acid is a selective lesioning agent (*5*), although we have no evidence of our own, others (*6*) have recently questioned the selectivity of kainic acid lesions. The nigrostriatal dopamine system, commonly used to test this selectivity, has cell bodies located in the substantia nigra and terminals that synapse in the striatum. Injections of kainic acid into striatum appear to damage the striatal dopaminergic axons and synapses, and histofluorescence of the striatum after such injections indicates extensive depletion of dopamine. Swollen varicosities indicative of degeneration of catecholamine axons and terminals can be seen. In contrast, histofluorescence of the caudate nucleus after infusion of MSG into the caudate reveals no damage to catecholamine terminals (*3*). A recent electron microscopic study (*7*) can also be interpreted as not supporting the specificity of kainic acid lesions. It has been shown that afferent striatal neurons, specifically including nigrostriatal afferents, make asymmetrically shaped contacts with dendritic spines (*8, 9*), whereas intrinsic striatal neurons make symmetrically shaped synaptic contacts. Hattori and McGeer (*7*) found both symmetrical and asymmetrical terminal degeneration. Thus, some of the synapses damaged by striatal injections of kainic acid may be terminals of nigral cell bodies. Thus, while kainic acid may be more neurotoxic than glutamate, it may not be as selective for cell bodies as MSG appears to be.

In our original report we indicated that the infusion of amino acids such as MSG holds promise as a fiber-of-passage sparing brain lesioning technique. Subsequent data have thus far supported this claim. We invite others to test further the selectivity of MSG lesions.

EARL L. SIMSON
RICHARD M. GOLD

Department of Psychology, University of Massachusetts, Amherst 01003

References

1. E. L. Simson, R. M. Gold, L. J. Standish, P. L. Pellett, *Science* **198**, 515 (1977).
2. E. L. Simson, R. M. Gold, P. E. Sawchenko, R. Eng, *Sixth International Conference on the Physiology of Food and Fluid Intake (Abstr.)* (1977).
3. E. L. Simson, L. Brown, R. M. Gold, in preparation.
4. E. L. Simson, *Eastern Psychological Association Abstr.* **49**, 183 (1978).
5. J. W. Olney, O. L. Ho, V. Rhee, *Exp. Brain Res.* **14**, 61 (1971); J. W. Olney, V. Rhee, O. L. Ho, *Brain Res.* **77**, 507 (1974); J. W. Olney, L. G. Sharpe, T. de Gubareff, *Neurosci. Abstr.* **5**, 371 (1975); J. T. Coyle and R. Schwarcz, *Nature (London)* **263**, 244 (1976); R. Schwarcz and J. T. Coyle, *Life Sci.* **20**, 431 (1977); E. G. McGeer and P. L. McGeer, *Nature (London)* **263**, 517 (1976).
6. R. C. Meibach, L. Brown, F. H. Brooks, *Brain Res.*, in press.
7. T. Hattori and E. G. McGeer, *ibid.* **129**, 174 (1977).
8. J. M. Kemp and T. P. S. Powell, *Philos. Trans. R. Soc. London Ser. B* **262**, 429 (1971).
9. T. Hattori, H. C. Fibiger, P. L. McGeer, L. Maler, *Exp. Neurol.* **41**, 599 (1973).

21 April 1978

0036-8075/78/0623-1417$00.50/0