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LETTER TO THE EDITOR

LASTING RECOVERY OF MOTOR FUNCTION, FOLLOWING BRAIN DAMAGE, WITH A SINGLE DOSE OF AMPHETAMINE COMBINED WITH PHYSICAL THERAPY; CHANGES IN GENE EXPRESSION?

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Animal studies (8) and pilot clinical studies (7) have demonstrated that combining amphetamine administration with appropriate motor activity results in sustained improvement in motor function in brain damaged rats and humans. The effect can be obtained with a single dose of amphetamine. Previously, Luria (12) had summarized a series of human studies from the Soviet Union, most of which related to the early and late treatment of soldiers injured in WW II, that also showed sustained motor function improvement following a single dose of Prostigmine. How the lasting effect can be produced with a single dose is not known.

Amphetamine can induce drug-specific activation of the c-fos gene in the striatum, via activation of the D1 dopamine receptors (11). Fuxe et al. (10) consider it likely that the D1 striatal receptors can activate the c-fos gene by increasing the formation of cAMP. In view of these and other recent findings, we suggest the possibility that the sustained improved motor function may be related to changes in gene expression. Demonstration of such a mechanism would have significant implications for understanding 1) the mechanisms of reorganization of function following brain damage; 2) the role of specific neuroactive substances (including neurotransmitters, neuropeptides and specific neuropharmacological agents to modify them) in the recovery process; and 3) the role of physical and other rehabilitation in the recovery.

The importance of basing the development of neurologic rehabilitation methods on an understanding of neural mechanisms has been discussed elsewhere (1), and a number of possible mechanisms have been examined (6), including those related to the effects of the active participation of the patient in the rehabilitation process on specific neuroactive substances (5).

The possibility that volume transmission (9) may be of importance has recently been evaluated (2, 3, 4); we add here the suggestion that the possible changes in gene expression may relate to synaptic as well as extrasynaptic receptor changes. In the latter case, volume transmission would have to be considered. For example, after a CNS insult, volume transmission may play a role in sustaining the "target" neurons in an active state, to prevent cell death due to denervation.

We suggest that it is necessary, at this early stage of development of theory-based neurologic rehabilitation, to speculate on possible relevant mechanisms. Such speculation should lead to experiments, which will in turn lead to more efficient and cost-effective neurologic rehabilitation.

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REFERENCES

1. Bach-y-Rita, P.: Theory-based neurorehabilitation. Arch Phys Med Rehabil *70:* 162, 1989.
2. Bach-y-Rita, P.: Thoughts on the role of volume transmission in normal and abnormal mass sustained functions. In: Volume Transmission in the Brain (ed. K. Fuxe and L. F. Agnati), pp. 489–496. Raven Press, New York, 1991.
3. Bach-y-Rita, P.: Receptor plasticity and volume transmission in the brain: emerging concepts with relevance to neurologic rehabilitation. J Neurol Rehab. In press *a.*
4. Bach-y-Rita, P.: Volume transmission in the brain, sensory substitution, and home stroke rehabilitation: emerging brain plasticity-related concepts in neurologic reha-

bilitation. In: Rehabilitation of the Neurological Patient (ed. L. S. Illis et al.), 2nd ed. Blackwell Publications, Oxford. In press *b*.

5. Bach-y-Rita, P. & Wicab Bach-y-Rita, E.: Hope and active patient participation in the rehabilitation environment. Arch Phys Med Rehabil *71:* 1084–1085, 1990.
6. Bach-y-Rita, P. & Wicab Bach-y-Rita, E.: Biological and psychosocial factors in recovery from brain damage in humans. Can J Psychol *44:* 148–65, 1990.
7. Crisostomo, E. A., Duncan, P. W., Propst, M., Dawson, D. V. & Davis, J. N.: Evidence that amphetamine with physical therapy promotes recovery of motor function in stroke patients. Ann Neurol *23:* 94–97, 1988.
8. Feeney, D. M., Gonzalez, A. & Law, W. A.: Amphetamine, haloperidol, and experience interact to affect rate of recovery after motor cortex injury. Science *217:* 855–857, 1982.
9. Fuxe, K. & Agnati, L. F.: Volume Transmission in the Brain. Raven Press, New York, 1991.
10. Fuxe, K., Agnati, L. F., Rosén, L., Bjelke, B., Cintra, A., Bortolotti, F., Tinner, B., Steinbusch, H., Gustafsson, J.-Å. & Benefati, F.: Computer-assisted image analysis techniques allow a characterization of the compartments produced by d-amphetamine activation of the c-fos gene. J Chem Neuroanat, in press.
11. Graybiel, A. M., Moratalla, R. & Robertson, H. A.: Amphetamine and cocaine induce drug-specific activation of the c-fos gene in striosome-matrix compartments and limbic subdivisions of the striatum. Proc Natl Acad Sci USA *87:* 6912–6916, 1990.
12. Luria, A. R.: Restoration of Function after Brain Injury. Pergamon Press, Oxford, 1963.

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