Restorative Neurology and Neuroscience 19 (2001) 157–158

Editorial

The structural and functional plasticity of the hippocampal formation

Julio J. Ramirez*

Davidson College, Davidson, NC 28035, USA

In his analysis of the scientific enterprise, Thomas Kuhn [10] remarked that "scientific revolutions are inaugurated by a growing sense…that an existing paradigm has ceased to function adequately in the exploration of an aspect of nature to which that paradigm itself had previously led the way [p. 92]." Within the neuroscience community, the late 1950s through the early 1970s proved to be a just such a period of scientific revolution. Despite the prevailing belief that the central nervous system (CNS) of adult mammals was resistant to changes in its connectivity (discussed in [7,8,21]), a handful of studies revealed that, on the contrary, when challenged with injury the CNS was a highly responsive self-reorganizing system. Just as axonal sprouting by intact fibers neighboring or sharing a terminal field of a pathway that has been injured was evident in the peripheral nervous system [5], so too in the CNS axonal sprouting proved to be the rule rather than the exception. Studies of the spinal cord by Liu and Chambers [11], of the brain stem by Goodman and Horel [6], of the septum by Raisman [17] and Moore, et al. [14], of the red nucleus by Nakamura et al. [15] and Tsukahara, et al. [22,23], for example, clearly demonstrate the near ubiquity of lesion-induced axonal sprouting in the adult CNS.

With the 2002 publication of this special issue of *Restorative Neurology and Neuroscience* (*RNN*), we mark the 30th anniversary of the publication of a seminal paper on the lesion-induced plasticity of the hippocampal formation: "Induced acetylcholinesterase-rich layer in rat dentate gyrus following entorhinal lesions" by Lynch, Matthews, Mosko, Parks and Cotman [13]. As described by Lloyd Guth [8] in his history of CNS regeneration research, "this system provides a remarkable model for studying collateral sprouting." In a similar vein, this year marks the 31st anniversary of the publication of yet another seminal paper in the area of activity-induced plasticity of the hippocampal formation: "Patterns of activation in a monosynaptic cortical pathway: The perforant path input to the dentate area of the hippocampal formation" by Lømo [12]. The Lømo report established an enormously heuristic model to empirically examine fundamental concepts in synaptic plasticity, including the Hebbian synapse [9].

With the contributions contained in this special issue, we celebrate the significant advances neuroscience has made in the last 30 years in providing a more fully developed elucidation of the factors underlying the plasticity of the hippocampal formation, a structure central to fundamental higher cognitive processes such as learning and memory (for review see [20]). The articles contained herein reflect the influence of these reports and indicate the future directions our discipline will explore.

Among the many issues confronting investigators interested in discovering how lesion-induced hippocampal sprouting might be regulated, the debate centered on whether sprouting is translaminar or restricted to specific spatial domains has been particularly rich. Within this special issue of *RNN*, review articles by Deller, Haas and Frotscher [4] and by Collazos-Castro and Nieto-Sampedro [3] persuasively argue that although hippocampal sprouting is quite active within lamina normally innervated by surviving afferents, the sprouting response is not translaminar. These authors explore the role of glial cells and their products (e.g., extracellular matrix molecules) in establishing the boundaries that may promote and repel axonal sprouting.

In their review, Bechmann and Nitsch [1] raise the important possibility that the immunologic response occurring in the CNS following an injury may have deleterious effects on axonal regeneration. Their investigations of the hippocampal response to the loss of the input emerging from the entorhinal cortex reveal a cascade of events suggesting a complex interaction of the adaptive immune system and the CNS' in-

* Corresponding address: R. Stuart Dickson Professor, Laboratory of Behavioral Neuroscience, Department of Psychology, Davidson College, Davidson, North Carolina 28035, USA. Tel.: +1 704 894 2888; Fax: +1 704 894 2512; E-mail: juramirez@davidson.edu.

nate immune system. Bechmann and Nitsch propose that developing means to control this interaction may provide fertile strategies for promoting recovery from CNS injury.

A robust feature of hippocampal function is the ability to exhibit long-term potentiation, a synaptic phenomenon that is often invoked as a neurophysiological model of learning and memory [19]. Colbert [2] focuses his review on a particularly exciting area of research wherein the back-propagation of the action potential up the dendritic arbor may serve as a key mechanism enabling Hebbian plasticity. As Colbert clearly underscores, back-propagation not only accounts for the temporal coincidence of pre- and postsynaptic activation, which would be a necessary condition for a Hebbian association, but also raises the intriguing prospect of how specific branches of a dendritic arbor might gain greater synaptic weight during learning.

In their explorations using an innovative brain injury model, Phillips and Reeves [16] assessed the structural, neurophysiological, and behavioral effects of combining a targeted deafferentation of the hippocampus (by damaging the entorhinal cortex) with a diffuse concussive brain insult. Their review indicates that concussive injury seriously disrupts the regenerative plasticity typically seen in the hippocampus after an entorhinal lesion thereby compromising the capacity to recover neurophysiogical and behavioral functions. They propose that strategies aimed at promoting recovery from head trauma should include pharmacological interventions that both blunt the excitotoxic consequences of head injury as well as facilitate synaptogenesis that may contribute to postlesion behavioral recovery.

Following the partial deafferentation of the hippocampus produced by a unilateral entorhinal cortex lesion, an intact homotypic input and several heterotypic inputs to the hippocampus undergo axonal sprouting. After reviewing the neuroanatomical, neurophysiological, and behavioral correlates of this lesion-induced axonal sprouting, Ramirez [18] notes that the likelihood of behavioral recovery increases as a function of the similarity of the remodeled neural system to the original neural configuration. Based on hippocampal literature of the last 30 years, Ramirez proposes that the interaction of homotypic sprouting, neurotrophic factors, and disinhibition may provide the foundation for functional reorganization. Consequently, developing multipronged therapeutic interventions targeting the interaction of these three elements may provide a particularly powerful approach to enhance recovery from CNS injury.

In closing, the articles contained in this special issue clearly reveal the tremendous advances that neuroscience has made in the last three decades. The intellectual terrain explored in these articles has yielded critical insights into the organization and function of the CNS. Perhaps the most exciting conclusion one can draw from this special issue is that biomedical science is poised to reveal the principles and mechanisms by which the CNS regulates lesion-induced plasticity as well as normal synaptic plasticity. The future will be rich with scientific discovery and with hope for victims of CNS injury.

References

[1] Bechmann, I. and Nitsch, R. Plasticity following lesion: Help and harm from the immune system. *Restor. Neurol. Neurosci.* **19** (2001) 189-198.

[2] Colbert, C.M. Back-propagating action potentials in pyramidal neurons: A putative signaling mechanism for the induction of Hebbian synaptic plasticity. *Restor. Neurol. Neurosci.* **19** (2001) 199–211.

[3] Collazos-Castro, J.E. and Nieto-Sampedro, M. Developmental and reactive growth of dentate gyrus afferents: Cellular and molecular sinteractions. *Restor. Neurol. Neurosci.* **19** (2001) 169–187.

[4] Deller, T., Haas, C.A. and Frotscher, M. Sprouting in the hippocampus after entorhinal cortex lesion is layer-specific but not translaminar: Which molecules may be involved? *Restor. Neurol. Neurosci.* **19** (2001) 159–167.

[5] Edds, M.V. Collateral nerve regeneration. *Q. Rev. Biol.* **28** (1953) 260–276.

[6] Goodman, D.C. and Horel, J.A. Sprouting of optic tract projections in the brain stem of the rat. *J. Comp. Neurol.* **127** (1966) 71–88.

[7] Guth, L. Axonal regeneration and functional plasticity in the central nervous system. *Exp. Neurol.* **45** (1974) 606–654.

[8] Guth, L. History of central nervous system regeneration research. *Exp. Neurol.* **48** (1975) 3–15.

[9] Hebb, D.O. *Organization of Behavior.* John Wiley & Sons, New York, 1949.

[10] Kuhn, T.S. *The Structure of Scientific Revolutions.* The University of Chicago Press, Chicago, 1970.

[11] Liu, C.M. and Chambers, W.W. Intraspinal sprouting of dorsal root axons. *Arch. Neurol. Psychiat.* **79** (1958) 46–61.

[12] Lømo, T. Patterns of activation in a monosynaptic cortical pathway: The perforant path input to the dentate area of the hippocampal formation. *Exp. Brain Res.* **12** (1971) 18–45.

[13] Lynch, G., Matthews, D.A., Mosko, S., Parks, T. and Cotman, C. Induced acetylcholinesterase-rich layer in rat dentate gyrus following entorhinal lesions. *Brain Res.* **42** (1972) 311–318.

[14] Moore, R.Y., Bjorklund, A. and Stenevi, V. Plastic changes in the adrenergic innervation of the rat septal area in response to denervation. *Brain Res.* **33** (1971) 13–55.

[15] Nakamura, Y., Mizuno, N., Konishia, A. and Stato, M. Synaptic reorganization of the red nucleus after chronic deafferentation from cerebellorubral fibers: an electron microscopic study of the cat. *Brain Res.* **82** (1974) 298–301.

[16] Phillips, L.L. and Reeves, T.M. Interactive pathology following traumatic brain injury modifies hippocampal plasticity. *Restor. Neurol. Neurosci.* **19** (2001) 213–235.

[17] Raisman, G. Neuronal plasticity in the septal nuclei of the adult rat. *Brain Res.* **14** (1969) 25–48.

[18] Ramirez, J.J. The role of axonal sprouting in functional reorganization after CNS injury: Lessons from the hippocampal formation. *Restor. Neurol. Neurosci.* **19** (2001) 231–262.

[19] Richter-Levin, G. and Yaniv, D. Is LTP in the hippocampus a useful model for learning-related alterations in gene expression? *Rev. Neurosci.* **12** (2001) 289–296.

[20] Squire, L.R. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol. Rev.* **99** (1992) 195–231.

[21] Stein, D.G., Brailowsky, S. and Will, B. *Brain Repair.* Oxford University Press, New York, 1995.

[22] Tsukahara, N., Hultborn, H. and Murakami, F. Sprouting of cortico-rubral synapses in red nucleus neurones after destruction of the nucleus interpositus of the cerebellum. *Experientia* **30** (1974) 57–58.

[23] Tsukahara, N., Hultborn, H., Murakami, F. and Fujito, Y. Electrophysiological study of formation of new synapses and collateral sprouting in red nucleus neurons after partial denervation. *J. Neurophysiol.* **38** (1975) 1359–1372.