LETTER TO THE EDITOR


Recently, Royo et al (1) nicely reviewed different approaches that may improve functional neurological outcome after traumatic brain injury; these ranged from inhibition of cell death, cell replacement strategies and stimulation of neurogenesis to blockade of axon growth inhibition and/or its operated intra-axonal signaling pathways. As outlined, axonal growth inhibition in the central nervous system (CNS) is considered to be a major barrier to axon regeneration and converges at the intra-axonal second messenger mechanism eliciting activation of the small GTPase RhoA (1). The Rho pathway is operated by growth inhibitors embedded in CNS myelin (myelin-associated glycoprotein [MAG], Nogo-A [Nogo-66], oligodendrocyte-myelin glycoprotein [OMgp]), and the glial scar (CSPG), as well as by putative repulsive guidance molecules (semaphorins, ephrin A5) and repulsive clotting proteases (Thrombin) present at the early lesion site (Fig. 1). Despite the enthusiasm of early attempts to develop clinical treatment based on animal research inhibiting Rho activation (2, 3), pitfalls have resulted from the neurotrophin approach (4). Identification of the plethora of biological actions moderated by Rho suggests indiscriminate flooding of the CNS lesion with Rho-inhibiting drugs is an obsolete therapeutic concept because of the putative initiation of serious side effects, such as paraesthesias and convulsive activity in man (4). This decisive statement can be made because the second messenger system Rho regulates survival, differentiation, and maintenance of neuron-specific characteristics, but is also

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Fig. 1.
instructive in modulating activity-dependent neuronal plasticity, essential for structural refinement of neuronal circuits in cortex and for learning and memory (5). Therefore, a note of caution seems to be appropriate and timely. Furthermore, since neurotrophins, guidance molecules, and nerve growth inhibitors share the same RhoA second messenger system (Fig. 1), the hierarchy for the navigating axon in CNS lesions remains unclear. Thus, understanding reasons for the failure of the neurotrophin trials is a suitable approach to render “Rho inhibition trials” more safe and efficient. Ongoing and future programs tailored towards prolonged and unspecific cell type RhoA inhibition—in transplanted or saved residual cells—as a target to promote CNS regeneration in human may take advantage of this note.

REFERENCES


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