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Growth-Regulated Proteins and Neuronal Plasticity

A Commentary

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Contents

Abstract

Growth-regulated proteins (GRPs) of the neuron are synthesized during outgrowth and regeneration at an increased rate and enriched in nerve growth cones. Therefore, they can be used to some degree as markers of neurite growth. However, these proteins are not unique to the growing neuron, and their properties are not known sufficiently to assign them a functional and/or causal role in the mechanisms of outgrowth. During synaptogenesis, GRPs decrease in abundance, and growth cone functions of motility and organelle assembly are being replaced by junctional contact and transmitter release. However, there is a stage during which growth cone and synaptic properties overlap to some degree. We propose that it is this overlap and its continuation that allow for synaptic plasticity in developing and adult nervous systems. We also propose a hypothesis involving (a) trophic factor(s) that might explain the regulation of synaptic sizes and collateral sprouting. Some GRPs, especially GAP43/B50/pp46/F1, are more prominent in adult brain regions of high plasticity, and they undergo change, such as phosphorylation, during long-term potentiation (LTP). Without precise functional knowledge of GRPs, it is impossible to use changes in such proteins to explain the plasticity mechanism. However, changes in these "growth markers" are likely to be an indication of sprouting activity, which would explain well the various phenomena associated with plasticity and learning in the adult. Thus, plasticity and memory may be viewed as a continuation of the developmental process into adulthood.

Index Entries: Growth cones; plasticity; memory; growth-regulated proteins; synaptogenesis.

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Introduction

The goal of this commentary is to reexamine the hypothesis that mechanisms of plasticity and long-term memory have their roots in developmental processes. The idea was proposed for the first time by the great visionary of neuroscience, Santiago Ramon y Cajal (1897). A long period of debate followed, but data obtained in recent years are increasing the enthusiasm for the concept (Pfenninger, 1986; Greenough and Bailey, 1988; Bliss, 1990; Rose, 1991; Wolpaw et al., 1991).

A relationship between developmental events on the one hand and plasticity and long-term memory in the adult nervous system on the other can be postulated on purely theoretical grounds, extrapolating from experimental data on development. The elegant pioneering work by Hubel and Wiesel and others (Constantine-Paton et al., 1990) established that development of neuronal circuitry is dependent on patterns of neuronal activity. Many experimental studies, e.g., Purves and Voyvodic (1987), demonstrated in the meantime that even in the adult nervous system, synaptic patterns and thus circuitry can be changed.

It follows that the developmental process leading to the establishment of neuronal connectivity is fit to modify the circuitry further—the process known as plasticity. As more data accumulate to indicate that the mature brain is not "hard-wired" and that there are changes in synapse numbers (e.g, Greenough and Bailey, 1988), this view is gaining strength. An increase in the number of synapses in a particular brain region implies—almost by necessity—a preceding process of neuronal sprouting. Actual proof for a role of sprouting in synaptic plasticity may come from biochemical studies that demonstrate changes in putative marker proteins of neurite growth and growth cones.

GRPs and Their Role in Growth Cone Function

Neurons go through at least three major phases of differentiation (Fig. 1). Initially, during a stage of proliferation, neuroblasts express a fully functional cell-cycle machinery. The terminal mitosis marks the neuron's "birth" and introduces a phase of neurite outgrowth characterized by the expression of a new set of gene products, including GRPs and other growth cone components.[†] Target cell recognition triggers synaptogenesis and thus the shift into the third stage, maturity (to be discussed below).

The major growth cone functions are amoeboid motility for pathfinding to the target area, target cell recognition, and assembly of organelles (Letourneau et al., 1992). Of particular importance is the assembly of cytoskeleton and plasma membrane, a prerequisite for neurite extension. It is not surprising that investigators have been attempting to link the appearance of GRPs during neurite outgrowth, their increased synthesis, and/or their enrichment in the growth cone to specific growth cone functions or the relevant regulatory mechanisms. The main GRPs of the neuron include GRP43 (GAP43, B50, pp46, F1; Skene, 1989), the 80-kDa C-kinase substrate MARCKS (pp80ac; Katz et al., 1985; Stumpo et al., 1989), 5B4-CAM (a member of the N-CAM family; Ellis et al., 1985), the proto-oncogene product pp60c-src (Maness et al., 1988), and a set of G proteins (Simkowitz et al., 1989; Edmonds et al., 1990; Strittmatter et al., 1990).

The specific functions in the growth cone are not known for any of these proteins. A further problem is that actin and tubulin synthesis and transport into the neurite and growth cone are also increased during neurite outgrowth (Simkowitz et al., 1989; Skene, 1989), so these very common molecules qualify equally well as GRPs. It is reasonable to postulate that all these proteins play important or perhaps essential roles in outgrowth and growth cone funtion. It is unreasonable, however, to assign to them a highly specific, causal role in the outgrowth process

[†]The term *growth-regulated protein* may be preferable to *growth-associated protein (GAP)*, as it suggests co-regulation with neurite outgrowth without implying a causal role in this process. Furthermore, the term *GAP* is now used more widely for *GTPase-activating protein*.

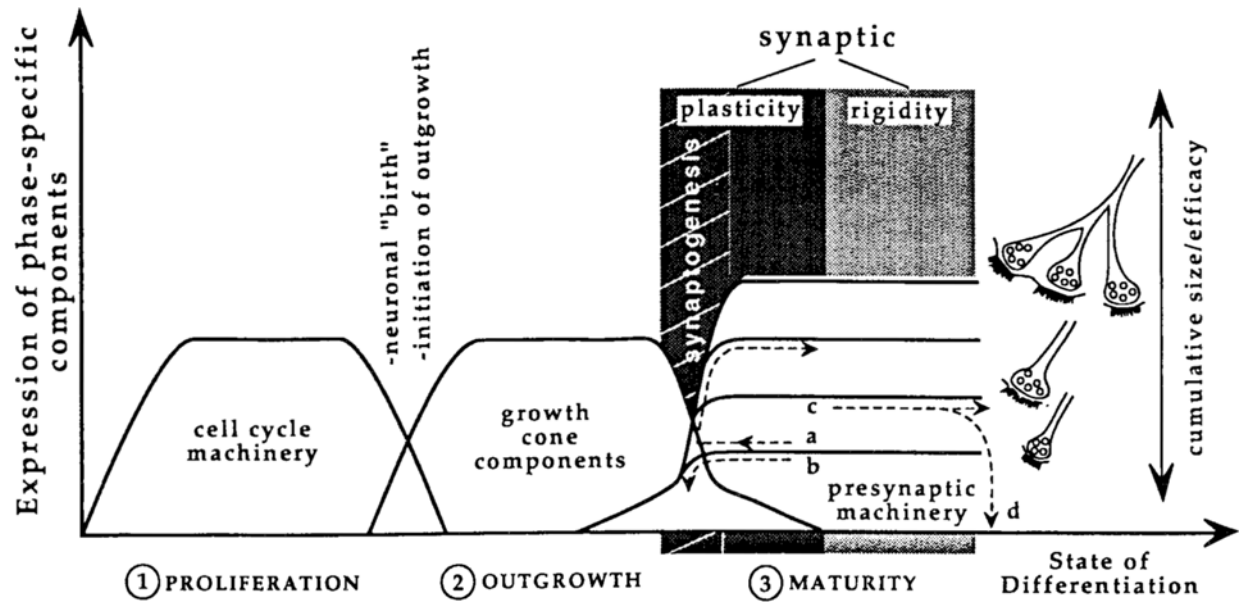

Fig. 1. Schematic representation of the major stages of neuronal differentiation. The expression of selected specific components is shown as a function of the state of differentiation. The shaded area highlights the synapsing, mature state of the neuron. Plasticity is viewed as a continuation of a phase during which components characteristic of and necessary for outgrowth and synaptic maturity are expressed simultaneously. Within that phase, synaptic size can be altered. For further description and discussion, and for explanation of a, b, c, and d, *see* text.

when their increased expression may be a consequence of neurite formation. Furthermore, at least some of the growth cone functions are not unique and can be found in other systems that exhibit amoeboid motility or vectorial growth. We should not be surprised, therefore, that none of the GRPs discovered to date are unique to the developing neuron. Yet, GRPs, especially when assayed as a group, may be used with caution as biochemical markers of neurite outgrowth.

Functional Shifts During Synaptogenesis

During synaptogenesis, the growth cone gives way to a new structure with a different function (Fig. 1). Outgrowth and motility are replaced by the function of a junction and transmitter release. It is not surprising, therefore, that many changes are observed in the proteins synthesized and transported to the nerve terminal during this transition. Such changes have been explored by several investigators, including Simkowitz et al. (1989), Larrivee (1991), and Wallis et al. (1992). As one might expect, GRPs (such as GRP43) are downregulated, while new ones, including certain synaptic-vesicle proteins, (e.g., synapsin I; Katz et al., 1985; De Camilli et al., 1990) appear. Yet, regulated exocytosis is a major function of both the growth cone and the presynaptic terminal. At the two stages of neuronal differentiation, however, it serves very different purposes. In the growing neuron, calcium-regulated exocytosis is required for plasmalemmal expansion, i.e., for the fusion of a cytoplasmic pool of plasmalemmal precursor vesicles with the cell surface (Lockerbie et al., 1991). This does not appear to be accompanied by transmitter release even though neurotransmitters can be taken up or synthesized by growth cones (Balcar et al., 1986; Taylor and Gordon-Weeks, 1989). In the

mature neuron, regulated exocytosis is necessary for transmitter release, but a net increase in plasmalemmal area has not been reported under normal conditions. It should be noted that plasmalemmal precursor vesicles and synaptic vesicles are different in size and probably protein composition; e.g., synapsin I is abundant in synaptic vesicles and endings but sparse in growth cones (Katz et al., 1985; De Camilli et al., 1990).

These considerations stress the relatedness of growth cones and presynaptic endings. This similarity as well as growth cones' limited ability to process neurotransmitter and the retention in synaptic terminals of small amounts of GRPs (note the overlap of the second and third phases of neuronal differentiation in Fig. 1) indicate that the transition from outgrowth to maturity is not sharp (Katz et al., 1985; Neve et al., 1988; De la Monte et al., 1989; Simkowitz et al., 1989; Theodosis et al., 1991). Quite to the contrary, there appears to be considerable overlap, which makes it easier to comprehend hypothetical shifts from synaptic function "back" to growth cone function and sprouting and vice versa.

Control of Synaptic Size and Number

The prevalence of a particular signal path in a neuronal circuit can be altered by changing the efficacy of the synapse(s) involved. This may be accomplished by modifying ion channel and/or receptor properties of the synaptic membranes (Kandel and Schwartz, 1982) or by changing synaptic size and/or number, i.e., the number of transmitter quanta released and the number of receptors. The latter phenomenon is likely to be slower, but once established, it may last for a long time without the need for a sustaining metabolic process, e.g., ongoing phosphorylation. Alterations in synaptic size and number necessitate coordinate changes of the pre- and postsynaptic elements. In this case, therefore, anyone who sees plasticity as a postsynaptic event will find "proof" for his/her hypothesis as easily as someone trying to test the hypothesis that plasticity is presynaptic!

There are now many studies available demonstrating that synapse numbers can be altered after their establishment (Constanine-Paton et al., 1990). For example, monocular deprivation in the cat leads to decreased synaptic numbers in the lateral geniculate nucleus (Tieman, 1991). A related, dramatic phenomenon is the sharpening of retinotopic projections in goldfish tectum (Schmidt, 1990). In that case, it is clear that it is not the amount but the pattern of activity that drives synaptic change, i.e., the deletion of certain synapses and the formation of new ones. The greatest degree of such plasticity is found during a particular time window in development, the "critical period" (Olson and Freeman, 1980), but it also varies a great deal from one brain region to the next. Interestingly, during the critical period and in the most plastic regions, expression of GRP43 is maintained at considerably higher levels than in other areas and developmental phases (Benowitz and Perrone-Bizzozero, 1991).

The establishment and maintainence of a synapse requires trophic interactions between pre- and postsynaptic elements. These may be surface-to-surface interactions and/or mediated by humoral signals. Figure 2 presents a simple cybernetic model for control of synaptic size or number involving a putative humoral factor that stimulates presynaptic sprouting and synaptogenesis. The presynaptic activity pattern controls the release of the factor from the postsynaptic dendrite, or perhaps from glia. Thus, the postsynaptic response pattern must be linked to the secretion of such a factor.

The factor is broken down or removed from the presynaptic ending's environment continuously, so that equal factor secretion and removal result in constant synaptic size. An increase in factor secretion, however, enlarges the synapse or stimulates the formation of additional synapses. A reduction in synaptic size or synapse deletion results from a decrease in or elimina-

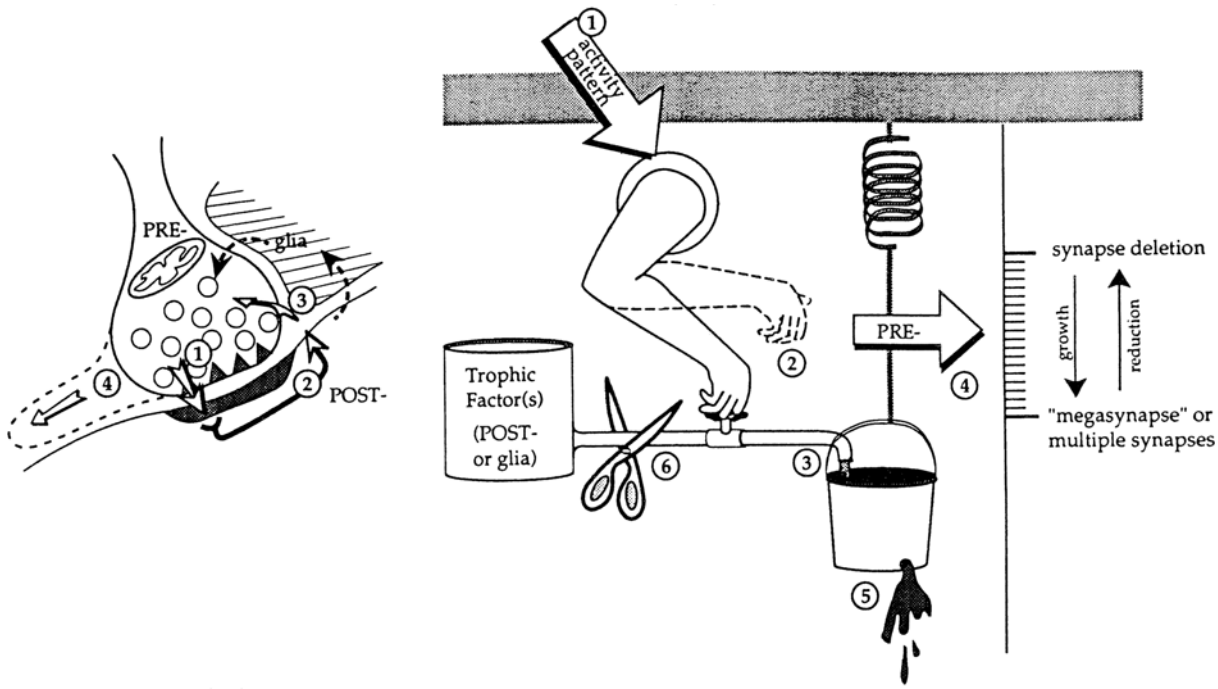

Fig. 2. Hypothetical cybernetic model of the regulation of cumulative synaptic size. The model involves the release of trophic factor(s) (3) regulated by the postsynaptic response (2) to presynaptic stimulation (1). Such trophic factor(s) stimulate axonal sprouting and increase synaptic size (4). However, if factor supply (3) and metabolism (5) are in balance, synaptic size is constant. Uncoupling of factor release from the postsynaptic response (2) or destruction of the synaptic target cell (6) leads to synapse deletion. For further description and discussion, *see* text.

tion of the factor, e.g., by destruction of the postsynaptic element. Potential uncoupling of factor secretion from this postsynaptic response pattern would result in the loss of synaptic plasticity, i.e., rigidity. Increasing evidence suggests the role of such (a) factor(s) in synaptic plasticity (Whittemore and Seiger, 1987; Terlau and Seifert, 1990; Houenou et al., 1991) as well as the participation of glia in the process (Muller and Best, 1989).

Returning to the phases of neuronal differentiation (Fig. 1, a–d), a rapid presynaptic sprouting response is possible only if the gene products necessary for outgrowth are readily available (note that the window of plasticity covers the time of overlap between outgrowth and maturity). Thus, by sending out a small sprout from an ending or a larger sprout from a more proximal point of the axon, a synapse can be enlarged or an additional synapse generated using the normal developmental processes (a). A synapse may also be deleted, followed by reinitiation of outgrowth and later synaptogenesis (b). Finally, a neuron's loss of growth cone components (c) will result in synaptic rigidity and, in the case of deletion of the synaptic contact(s) (by postsynaptic cell death or loss of trophic factor), in presynaptic cell death (d).

Growth Cones, Plasticity, and Memory

Early morphological studies on plasticity and learning that claimed changes of synaptic numbers or patterns were surrounded by much

controversy. More recent studies, however, especially those by Greenough and collaborators have established unambiguously that synapse numbers change concomitant with long-term learning (Chang and Greenough, 1984; Black et al., 1990; Glanzman et al., 1990; Bailey and Chen, 1991). As already indicated, an increased number of synapses almost certainly necessitates neuronal sprouting activity. A learning-associated increase in the numbers of neuronal sprouts (especially filopodia) was discovered recently by Robertson's laboratory in *Octopus* brain (Robertson and Lee, 1990). Not surprisingly then, LTP and long-term learning necessitate protein synthesis, and increases in glycoprotein and tubulin synthesis (growth of plasmalemma and cytoskeleton) have been reported (Rose, 1991).

There are several reports on the activation of immediate early response (IER) and related genes in the context of plasticity and learning, but the specificity of such gene activation is not clear at this time (Morgan and Curran, 1991). An interesting hypothesis was proposed recently by Walters et al. (1991). Similarities between mechanisms of learning and repair after nerve injury in *Aplysia* led these authors to suggest that memory may have evolved from the latter process. Of further interest is the observation that inhibition of phospholipase A_2, the major enzyme involved in (poly)phosphoinositide metabolism in growth cones (Negre-Aminou and Pfenninger, 1991), with bromophenacyl bromide reduces LTP formation in the adult hippocampus (Massicotte et al., 1990).

If sprouting occurs during LTP or learning, then GRPs should change or increase in appropriate neurons during that time. Indeed, GRP43 phosphorylation, as measured in a test-tube assay after stimulation of the brain, increases markedly with LTP (Lovinger et al., 1986). It is significant that a second GRP, MARCKS, also appears increasingly phosphorylated under the same conditions (Nelson et al., 1989). Even though we do not know the functional significance of GRP43 and MARCKS phosphorylation in sprouting, the correlation is striking. Clearly, levels and changes of other GRPs must be investigated in the same paradigm. Nevertheless, increased phosphorylation of MARCKS and GRP43 suggests that these GRPs are used in a function related to the establishment of LTP, i.e., that sprouting occurs during this process. It should be noted that no effort is being made here to explain LTP in molecular terms based on this finding but that increased phosphorylation of GRP43 and MARCKS is interpreted as an "epi-phenomenon" indicative of the sprouting process.

Summary

Most of the hypotheses dealing with the mechanisms involved in synaptic plasticity are rather polarized, focusing either on pre- or postsynaptic events, especially on channels and receptors present in one or the other membrane. Clearly, the initiation of a plastic change has to be separated from its product. If activity patterns of the synaptic input are important, as the evidence indicates, it is logical that the appropriate receptors, e.g., *N*-methyl-D-asparate (NMDA), play a critical role in the early phenomena (Constantine-Paton et al., 1990; Schmidt, 1990; Wolpaw et al., 1991). For a long-term increase in synaptic efficacy, the data summarized here seem to suggest an increase in synaptic size or number. This involves a sprouting process presynaptically as well as coextensive elaboration of the postsynaptic domain.

Such a change would alter channel and receptor parameters both pre- and postsynaptically, including the NMDA receptors. Axonal sprouting may well be stimulated by a factor or factors released from the postsynaptic element or even glial neighbors of the synapse (Whittemore and Seiger, 1987; Muller and Best, 1989; Terlau and Seifert, 1990; Houenou et al., 1991). Evidence for this model seems to be increasing, and the hypothesis has the great advantage that plasticity does not require a new mechanism but relies

on a process already established for the development of neuronal circuitry. If we accept the view that neuronal circuitry with synapses of specified efficacy represents a form of information storage, then plasticity, i.e., the modification of this circuitry and synaptic efficacy, is (a form of) long-term memory—a widely held view.

Therefore, long-term memory may be an extension of a developmental process into adulthood and may be based on mechanisms of neurite sprouting and synaptogenesis. The evidence for or against this model will have to come from studies with more reliable markers of neurite outgrowth. If this model is correct, the molecular mechanisms underlying long-term memory will be explored most successfully in developmental systems where neurite sprouting is prevalent.

Acknowledgments

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