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MECHANISMS OF AXONAL PLASTICITY

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INTRODUCTION

The elongation of neuronal processes is important not only during development to shape the architecture of the mature brain, but also during reparative processes after injury and in several forms of physiological plasticity. In the adult peripheral nervous system both axonal elongation and terminal and collateral sprouting are well known phenomena. However, in the central nervous system, while collateral sprouting occurs in several brain regions (44, 52), axonal elongation is hampered by several factors that depend both on intrinsic properties of the neurons and on the environment (4, 24). Intrinsic properties vary among neurons, as shown by the fact that distinctive axonal populations show different growth capabilities when confronted with similar environmental conditions (5, 6, 11, 24, 43). The main environmental factors that impede axon growth are the glial scar at the lesion site (4, 33, 40), myelin associated growth-inhibitory molecules (47, 48) and lack of growth-permissive promoting substances that are instead present in the peripheral nervous system (4, 19).

Several proteins are expressed during development in association with axonal elongation and some of them are reexpressed during the reparative processes after injury in the mature brain (14). One of the most deeply investigated proteins of this group is GAP-43 also called B-50 (review: 26, 39). This protein is widely expressed in the brain during development and in most neurons it is downregulated at the time of synaptogenesis (49). However, in several neuronal populations both in the peripheral (34, 51, 56) and in the central nervous system (7, 8, 20, 38, 40) the expression is maintained in the adult. It has to be underlined that *in vivo* it appears to be localized mainly into the axon terminals (21, 25).

This protein is strongly associated with nerve regeneration (9, 49). While in the peripheral nervous system an overexpression is commonly associated with axotomy, this is not always true for the central nervous system. Peripheral nerve graft onto an optic nerve sectioned at about one millimeter from the eye results in regeneration of the retinal axons (57) and overexpression of GAP-43 (22). A similar overexpression is also detected in cells that do not regenerate into the graft, but all regenerating cells do overexpress GAP-43 (46). In contrast, when nerve section is more distally placed no regeneration (57) and no GAP-43 overexpression occur. This means that while GAP-43 is potentially active in promoting regeneration, this protein alone might be not sufficient without other factors to allow elongation of axonal processes.

More recent work has shown that a key role of this protein is to modulate