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Review

Cerebellar grafting in the oculomotor system as a model to study target influence on adult neurons

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Abstract

In the last decades, there have been many efforts directed to gain a better understanding on adult neuron–target cell relationships. Embryonic grafts have been used for the study of neural circuit rewiring. Thus, using several donor neuronal tissues, such as cerebellum or striatum, developing grafted cells have been shown to have the capability of substituting neural cell populations and establishing reciprocal connections with the host. In addition, different lesion paradigms have also led to a better understanding of target dependence in neuronal cells. Thus, for example, axotomy induces profound morphofunctional changes in adult neurons, including the loss of synaptic inputs and discharge alterations. These alterations are probably due to trophic factor loss in response to target disconnection. In this review, we summarize the different strategies performed to disconnect neurons from their targets, and the effects of target substitution, performed by tissue grafting, upon neural properties. Using the oculomotor system—and more precisely the abducens internuclear neurons—as a model, we describe herein the effects of disconnecting a population of central neurons from its natural target (i.e., the medial rectus motoneurons at the mesencephalic oculomotor nucleus). We also analyze target-derived influences in the structure and physiology of these neurons by using cerebellar embryonic grafts as a new target for the axotomized abducens internuclear neurons.

Theme: Development and regeneration
Topic: Regeneration

Keywords: Oculomotor system; Abducens nucleus; Single-unit recording; Neuronal injury; Axonal sprouting; Cerebellar embryonic tissue

Contents

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1. Introduction

During the last years, increasing evidence has emerged, pointing out the role of target-derived neurotrophic factors as key mediators in the maintenance of neuronal phenotype in the adult central nervous system (CNS), regulating numerous functions such as synaptic plasticity [13,69,102], membrane excitability [32,46,129], synaptic input patterns and synaptic efficacy [80], as well as morphological properties, such as soma size and dendritic branching pattern [108].

In the adult nervous system, target disconnection produces different consequences depending on the severity of the lesion. First, functional target disconnection has been achieved using several neurotoxic agents, such as colchicine, an alkaloid that interrupts axonal transport by avoiding microtubule polymerization and thus blocking trophic communication [95]; or *Botulinum* neurotoxin, an endopeptidase that blocks neurotransmitter release in cholinergic terminals [101]. Also, neurons may lose their retrograde trophic support after selective removal of their target cells, for instance by using *Ricinus communis* lectin [27,28] (see Fig. 1).

Under several experimental manipulations, neurons respond in a similar manner to the loss of target-derived molecules, presenting a variety of modifications in their properties that last as long as trophic support is prevented [27,28,68,107]. These modifications include the reduction in soma size [27,107], the formation of varicosities in terminal dendrites, and a reduction in axonal and dendritic arborizations [27,68]. Some authors have also described afferent input withdrawal related to a reduction in synaptic potential amplitude [27,91].

Secondly, a more drastic method for neuron–target disconnection has been axotomy. This kind of lesion leads to a wider spectrum of alterations, with different degrees of severity depending upon the cell population [20]. Therefore, while some neuronal types degenerate or may even die after axotomy [57], other neurons survive [33,87]. Surviving neurons, however, exhibit marked changes in their structural and functional properties. For example, some populations suffer a series of characteristic morphological changes, the so-called chromatolytic reaction [7,67]. Other authors have described a reduction of the dendritic arbor [16,119] and a massive withdrawal of synaptic inputs [14,23,87].

These morphological modifications are normally accompanied by cell metabolism transformations, in a way that the neuron biochemical machinery moves from an operational mode (implicated in synaptic current integration, action potential conduction, or neurotransmitter release) to a regenerative mode, involved mainly in the process of membrane repair, remyelinization, or growth cone guidance. Thus, there is a reduction in the expression of genes related to neurotransmitter synthesis and release [94], while there is an up-regulation in the expression of structural and regeneration-related proteins [1,48]. There is also an increase in the expression of neurotrophin receptors [35,50,94].

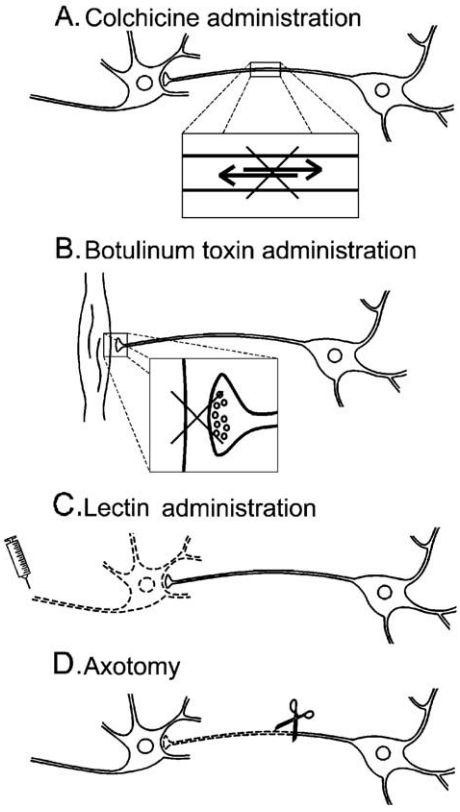

Fig. 1. Experimental tools for target disconnection. Several approaches have been used in order to disconnect a given neuron from its target cell. First, colchicine administration interrupts axon traffic. Consequently, neurons are deprived of retrogradely target-derived trophic support (A). *Botulinum* neurotoxin blocks neuromuscular synapses, producing the functional disconnection between the motoneuron and its target muscle (B). The administration of the cytotoxic ricin into the muscle leads to motoneuronal death. Therefore, central premotor neurons are left deprived of their target motoneurons (C). Finally, axotomy has been widely used in the study of target influence on afferent cells (D).

Besides structural and metabolic modifications, and, possibly, as a part of the same mechanism, lesioned neurons suffer alterations in their physiological properties, related with both membrane electrical properties [34,64] and synaptic transmission [31,34,64]. These transformations lead to profound modifications in neuronal firing properties, as shown in abducens motoneurons [31] and internuclear neurons [29].

Changes derived from peripheral axotomy are normally transitory due to the capacity of peripheral axons to regenerate. Thus, the properties of lesioned neurons resume to normality after target reconnection [16,31]. In central neurons, to the contrary, regeneration is impeded; thus, sectioned neurons cannot reestablish synaptic contact with their targets, and axotomy-derived modifications are permanent [7,29].

2. Embryonic grafts as an alternative target for lesioned neurons

In order to study target influence in the maintenance of adult neuron properties, some investigators have used