Review Article

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Nelson F. Annunciato (*University of Sao Paulo, Brazil*)

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Plasticity of the Nervous System

Nelson F. Annunziato, Ph.D.
Neurobiology Laboratory, Department of Histology
University of Sao Paulo, Brazil

This review presents evidence for possible recovery mechanisms after various forms of lesion in the central and peripheral nervous system. Implications for treatment strategies for patients with oral myofunctional disorders are discussed.

The above title will certainly raise some questions: (a) What is and for what purpose do we have neuronal plasticity?; (b) How can we use this knowledge to delineate therapeutic strategies in cases of nervous system (NS) damage?; (c) How can we explain NS participation in the modification of muscle tone?; (d) Should it be thought that only some patients up to or after certain ages can benefit from the plastic processes of the NS?; (e) Is it possible that only patients with damage in the NS have the potential of acquiring new neural circuits capable of improving certain functions?

We will consider some examples from recent publications on neural plasticity, to at least partially answer these questions.

When we talk about neuroplasticity we should initially have in mind that plasticity of the NS does not only occur in pathological conditions, but also assumes extremely important roles in the normal functioning of the organism. Here, for example, we can cite the important organization of nerve connections, which takes place during the embryonic development of the individual (Schäfer, 1991).

Many of these connections, are not only determined by the genetic program. Later on, in the developing child and adult, neuronal functions of "adaptation" will depend on environmental conditions. One of the first forms of neuronal plasticity is frequently called the "stimulus dependent maturation" (epigenetic factors) of the NS. A second form of plasticity in a normal organism can be understood as a "learning process", which involves both unconscious motor learning (unconscious neuromuscular memory [automatism]) and conscious learning (memory). The two processes are based on similar physiological mechanisms and constitute a base for the neural organization of the NS, as well as for rehabilitation after damage processes. What makes these processes especially interesting is the fact that they are directed by neural activity and, in consequence are influenced by peripheral stimulation, as all the

perceptions of our body and surroundings are captured and conducted to the neuro-axis by the sensory systems.

BASIC REORGANIZATION MECHANISMS

As is well known, mammals do not produce more nerve cells after final individual development. This fact can mislead us into thinking that the nervous system is static and unchangeable, and lacking regeneration mechanisms. However on the microscopic level the NS can be regarded as an intricate and complex dynamic network, whose function is to interpret the multiple connections among the nerve cells. Thus, we should start from the principle that reorganization and rehabilitation of neural functions also require an alteration to this neural network, in particular of NS interconnections. So we have the following possibilities: (a) recovery of synaptic effectiveness; (b) synaptic potentiation; (c) increase in sensitivity of deafferented cells; (d) persistence of hyper-innervation; (e) recruitment of "silent" synapses; (f) regenerative sprouting and collaterals; (g) adaptations.

(A) RECOVERY OF SYNAPTIC EFFECTIVENESS (FIG. 1).

After a stroke, trauma or surgery of the NS, many synapses become inactive, simply from being close to the damaged area, and the edema that surrounds it. Within one or two weeks, when the edema has considerably diminished, there is a striking recuperation of motor, cognitive and sensory functions.

(B) SYNAPTIC POTENTIATION (FIG. 2).

When some collaterals of an axon are damaged, all the neuroactive substances (neuromodulators and neurotransmitters), produced in its cell body, are transported to the intact terminals, thus increasing their stock. As an interesting example, we can cite what happens when a striated muscle is partially denervated. The myoneural junctions (motor end plates) not affected by the lesion show a pronounced increase in their acetylcholine content, resulting in nerve terminals with greater synaptic efficiency.

Figure 1 - Recovery of synaptic effectiveness. A, edema blocking conduction. B, conduction resumes when edema subsides. (Modified from FITZGERALD, 1985)

Figure 2 - Synaptic potentiation. A, transmitter passes from cell body to all terminals. B, reduction of anoxal territory may cause transmitter to accumulate in the surviving synaptic boutons. (Modified from FITZGERALD, 1985)

(C) INCREASE IN SENSITIVITY OF DENERVED CELLS (FIG. 3).

The removal of synaptic afferents is followed by the additional appearance of receptors in the post-synaptic membrane. These new receptors have the capacity to respond to neuroactive substances which are synthesized by neighboring terminals. A classic example is the increase in sensitivity of the striatum neurons to dopamine, which takes place after degeneration of some dopaminergic cells (nigro estriatal) as happens in Parkinson's disease.

(D) PERSISTENCE OF HYPER-INNervation (FIG. 4).

The NS of all mammals has, during embryonic development, an extremely high number of nerve cells. It is estimated that this number is 50% to 60% greater during development than in adults. Cells that establish adequate connections during a critical period, thus maintaining their appropriate functions, will survive, while the others eventually disappear due to a competitive mechanism. However, normal interferences in these competitive interactions can rescue some of the neurons that otherwise would die.

An example of what has been described above was

reported by Levay et al. (1980), in an experiment done with monkeys. The visual cortex of these primates is divided into various columns, so that each one of these columns receives in alternating fashion, fibers from only one eye. Until the sixth postnatal week there is an overlapping of fibers belonging to both eyes. After this period, the columns dominated by the left or the right eyes have become differentiated. If one of the eyes is closed (by suturing the eyelid) before the end of the third week, the columns dominated by the opened eye will become double their size in the sixth week, while the columns previously innervated by the closed eye will shrink to half of their original size. This finding is not a consequence of the growth of new fibers, but is due to persistence of fibers which, under normal circumstances, would have degenerated.

This type of observation gives us a scientific rational for treating children who, between one and two years of age, already have one dominant eye (a pathology known as "amblyopia"). If nothing is done to correct it, the cortical representation of the non-dominant eye will become suppressed. The usual treatment is therefore to cover the dominant eye to promote the normal development of the columns related to the other eye. It is evident that the dominant eye should be uncovered at regular intervals so as to find an adequate

Figure 3 - Denervation supersensitivity. A, target cell innervated by two axons. B, depleted innervation results in supersensitivity to reduced supply of neurotransmitters. Modified from FITZGERALD, 1985)

equilibrium in the development of the dominance columns.

(E) RECRUITMENT OF "SILENT" SYNAPSES.

Many parts of the NS possess, morphologically, synapses which appear to be inactive under normal physiological conditions. For example, when a lesion is made in the right cortical motor area in monkeys (which represents the left hand due to crossing of motor fibers), there follows an almost total inability to move the left hand (which is under the control of the right hemisphere which was damaged). In spite of this, a few weeks later, we can note a definite improvement of movements in the affected hand. If now, the right motor cortex is evaluated again, one notes that stimulation of areas adjacent to the damaged site will produce right hand movements. If these new areas which have begun to represent the hand are destroyed, there will be a severe and permanent paralysis of the hand. In short, we can say that the NS has mechanisms which strengthen connections which until now were "little used" or "weakly manifested".

(F) REGENERATIVE AND COLLATERAL SPROUTINGS (FIGS. 5 & 6).

Sprouting signifies new growth of neurites (dendrites and axons), which may be regenerative or collateral. In the first case (fig. 5), when an axon is damaged along its course, or if the target has been destroyed, short sprouts can appear approximately 100 Åm) and form new synapses in their vicinity. In the second case (fig. 6), neurons which have been deafferented can acquire the capacity to attract sproutings from neighboring nerve cells.

In the central nervous system (CNS), there can be as much sprouting of the undamaged cells as the damaged ones in the lesioned site. This means that intact neurons of the functional system, as well as neurons of other intact systems are involved in this process. We can find a good example in the red nucleus, found in the brain stem and related to the "extrapyramidal system". Fibers coming from the cerebral cortex and from the cerebellum make synapses with the red nucleus neurons. If the cerebellar fibers are damaged, the terminals from the sensory-motor cortex will grow and occupy synapses previously occupied by lesioned ones (Lund, 1978). Besides the observed modifications in the area surrounding the new synaptic contacts,

Figure 4 - Persistence of hyperinnervation. A, usual arrangement in perinatal period. B, normal adult neuron, with reduced innervation. C, partial denervation in childhood may allow additional boutons to persist. (Modified from FITZGERALD, 1985)

Figure 5 - Regenerative sprouting. A, destruction of target cell and afferent terminals. B, sprouting (arrow) of the injured axon into a different target cell. (Modified from FITZGERALD, 1985)

Figure 6 - Collateral sprouting. A, lesion causes depletion of afferents to one target cell. B, uninjured neuron sprouts (arrow) to supply the deafferented cell. (Modified from FITZGERALD, 1985)

regarding the number and size of the dendrites, modifications of the same kind can also occur as far as the spinal cord (Brown et al., 1979). The spinal cord sprouting takes place some days after the damage and continues for many weeks.

Sprouting can also be observed in the peripheral nervous system (PNS). In the periphery, particularly in the mixed nerves, "repair mechanisms" are responsible for controlling the sprouting of axons which were completely severed. Recent studies (Da-Silva et al., 1985) added new data concerning the reorganizational capacity of the PNS. In their experiments, the sciatic nerve was cut and a tube was placed between the distal and proximal stumps, bridging a gap distance of 4 mm. Four weeks after tube implantation, myelinated axons were present in the distal stump! Most of the sensory and motor neurons in the spinal ganglia and spinal cord could be labelled by a track solution injected in the distal stump.

After nerve damage there is rapid degeneration of the axons in the distal nerve stump, due to disconnection from their cell bodies. Axons from the proximal stump, which are connected to their cell bodies, rapidly start to branch, forming sprouts that grow along the myelin sheath forming cells (Schwann cells) that can guide them to their final places in the muscles or in the sense organs. This process is directed to reestablish the original functions. In case of a nerve that has only been crushed, the axon growth takes place along "correct" Schwann cell rows. On the other hand, after a nerve transection, axonal growth may occur along "incorrect" Schwann cells, leading the regenerating axons to non-original target organs. If this mismatch occurs, the only chance of a compensation would be through a possible central plasticity, (in the cortex, for example).

The regenerative process in the PNS described above can be observed even at considerable distances. However, in the CNS, in different cortical and subcortical structures, the elongation of damaged cells, does not occur when long distances are involved.

(G) ADAPTATIONS.

Some strategies may be used to lessen some neurological deficiencies. One example occurs with patients with homonymous hemianopsia, resulting from damage to one of the optic tracts, thus severing fibers from the temporal retina to the same side eye and fibers from the nasal retina of the opposite eye; with such a lesion the patient can see neither the nasal half of the visual field of one eye nor the temporal half of the visual field of the other eye. However, they can read normally by adapting themselves to this deficit by rotating their head a little, so that the page falls in the non affected visual field. Similar compensation also occurs frequently with patients with paralysis of the deltoid muscle, who

despite their handicap still manage to raise their arm by rotating the scapula with the spared muscles. There are various ways to adapt to neurological deficiencies or disfunctions. In the majority of cases, the adaptations come through involuntary and unconscious mechanisms.

THE SIGNIFICANCE OF PLASTIC MECHANISMS FOR THERAPEUTIC MEASURES.

In the preceding paragraphs, mechanisms which constitute the reorganizational basis for neural functional rehabilitation have been described. We have seen that the basic genetic program of an individual requires numerous environmental influences (epigenetic factors) in order for the neural circuits to develop, stabilize and perfect their functions. The processes of reorganization occur at different levels:

(I) Processes of reorganization macroscopically observed: (a) alteration of cortical fields; in the case of only a part of the field being affected, the functional and homogeneous part that remains being able to reestablish the function of the lost or injured part; (b) other areas can also lead to a functional restoration, especially when the function involved is common to both areas.

(II) Microscopic processes which take part in neural plasticity: (a) initial inhibition of connections immediately after damage; (b) local sprouting of compromised axons as well as of neighboring axons, leading to the formation of new synapses; (c) differentiation, stabilization and potentiation of functionally "correct" synapses; (d) recuperation of synapses which have lost their activity; (e) increase in sensitivity of denervated cells and persistence of hyperinnervated ones.

It is possible to conclude, based on the above findings, that, the sensory-motor stimulation of therapeutic exercises can be as significant as the spontaneous development or recovery of NS function. The principle goal is to reestablish functions in their own field, and for this the NS should be supplied with adequate and correct stimulation, so that it may learn (or relearn) to decode the information derived from the periphery, that it may process it, store it, most significantly, integrate it with other areas of the nervous system.

It is suggested that every therapeutic process should have as its aim the furnishing, through peripheral stimulation, of information of crucial importance in the organization of neural circuits, responsible for the neuromuscular control of the individual. One must be attentive to the fact that, if an imbalance or disfunction in this neuromuscular control, as for example hypotonicity of the orofacial musculature, atypical swallowing etc. has already taken place, one should

produce, therapeutically, a reorganization of sensory-motor activity to set in action the mechanisms of the plastic process of NS.

It is to be expected that the basic reorganizational mechanisms have less efficiency with the passing of the years; however there is no way one can say that this process has stopped definitely and irremediably at this or that age. The plastic process, even though physiologically or traumatically weakened, lasts even into old age. It is logical that therapeutic measures should start early on, in the sense of attempting to avoid greater abnormality in the development and stabilization of neural circuits. Here one should make clear that the term "early" refers only to therapeutic treatment at early ages, when this shows itself to be necessary, as, for example, in children who start to present incorrect posturing of the lips, mandible or tongue. This should not be confused with therapeutic strategies in which the patient receives stimulation beyond the appropriate chronological or neurological age as, for example, to attempt teach a three years old child to read, write and do mathematical calculations.

The nervous system is a complete indivisible unit, which is separated only for didactic ends. We should assess and treat the patient as a whole, supplying, in this way, the correct epigenetic information and stimuli. In recent years we have seen an increasing interest in observing and treating the total body posture of the orthodontic patient. The classic case is the patient with retrognathia that is frequently associated with many postural adaptations to mouth breathing. For example: forward head posture, alterations in the normal spine curves and position of the pelvis). These patients will need a combined oral myofunctional and physical therapy approach. These therapeutic methods which take into account the integrative phenomenon of the NS and the historic view of the patient, are based on the fact that sensory-motor development happens simultaneously with three ongoing processes: (a) an existing skill is "practiced"; (b) a function which has already been mastered, will be differentiated and perfected; (c) a new task will be embarked on (connections with trial and error experiments) (Stemme & Laage-Hellman, 1990).

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Address Correspondence to:
Dr. Nelson Francisco Annunciato, Ph.D.
Rua Euclides Pacheco, 803
03321-000 Sao Paulo - SP
Brazil