The spinal cord as organizer of disease processes: IV. Axonal transport and neurotrophic function in relation to somatic dysfunction

IRVIN M. KORR, PH.D.
Fort Worth, Texas

Among the neural phenomena important to musculoskeletal problems are the transport and exchange of macromolecular materials. Evidence for the trophic function of nerves includes examples of the atrophy of denervation in organs, of the way nerves influence morphogenesis, genic expression, and regeneration, and of nerve-to-muscle transmission. Research supports the view that the trophic influence of nerves on target organs depends largely on delivery of specific neuronal proteins by means of axonal transport and junctional transfer. There is also retrograde transport from nerve endings to cell bodies. Factors such as nerve or root deformation and hyperactivity of peripheral neurons may adversely affect trophic influences, resulting in aberrations of structure, function and metabolism, and, ultimately, somatic dysfunction. The effectiveness of manipulative therapy is probably due largely to its amelioration of trophic factors. Further investigation of the role of axonal transport and neurotrophic factors in somatic dysfunction is urged.

The most distressing consequences of biomechanical impairments of the musculoskeletal system that are amenable to manipulative therapy are those mediated by the nervous system. These consequences include pain and sensory manifestations and motor and autonomic disturbances. These manifestations are related to disturbances in excitation and conduction, that is, in impulse traffic. The impulse-based mechanisms underlying these clinical manifestations have been under study for many years. They seem to be initiated in two main ways: (1) altered sensory input from affected muscles, tendons, ligaments, and joints; and (2) direct insult to nerves and nerve roots.

Another category of neural phenomena, however, also has bearing on musculoskeletal problems, their manifestations, and their manipulative treatment. I refer to nonimpulse mechanisms based, not on the transmission of signals, but on the transport and exchange of macromolecular materials; namely, axonal transport and neurotrophic relations between neurons and target cells. Although these phenomena have been under intensive study, their relation to biomechanical problems and manipulative therapy has thus far received only speculative attention.[1,2] I am convinced that this is a most important area for clinical and fundamental investigation.

Although axonal transport and trophic function of nerves are not truly "organized" by the spinal cord, they are appropriate subjects for this series because most of the peripheral neurons are cord-derived and cord-connected. The spinal cord, therefore, may be said to be responsible through its organization for patterning trophic function also,[3] as well as those influences discussed in the preceding papers of this series.[4,5]

The purposes of this paper are as follows: (1) to illustrate the trophic functions of nerves; (2) to review some aspects of axonal transport and its relation to trophic function; and (3) to examine the vulnerability of axonal transport to biomechanical impairment and the kinds of clinical consequences that may be expected.

Trophic function of nerves

It is only in recent years that neuroscientists have ceased to be self-conscious and apologetic about the use of the word "trophic" in connection with nerves. So long had it been assumed that all neural phenomena could be explained in terms of impulses, electrical potentials, and frequencies (and the neurotransmitters released by impulses) that it was disconcerting to be confronted repeatedly with

mysterious but undeniable neural influences on target tissues that could not be related satisfactorily to impulses and reflexes. Following are a few examples:

1. *Atrophy of denervation.* The most thoroughly studied example, known for many centuries, is the atrophy (exemplified by anterior poliomyelitis) that skeletal muscle undergoes following denervation. This aspect of neurotrophic function has been admirably reviewed by Guth[6] and Gutmann.[7] Long attributed to the inactivity ("disuse") that follows interruption of the motor impulses, it is now well established that the atrophy of denervation is quite a different phenomenon from the atrophy of disuse (such as that following tenotomy or casting of extremities), even though, *because* of the disuse following nerve section, there are some features in common.

The critical factors are not the streams of impulses to the muscle and the contractile activity that they provoke, but the integrity of the connection between nerve cell and muscle cell via axon and myoneural junction—whether or not impulses are being or *can* be transmitted to the muscle. That it is a matter of connectedness between the two kinds of cells (neither of which can function without the other) is clearly substantiated by the denervation of certain sensory organs, (for example, the circumvallate papillae of the tongue). Sensory organs, of course, are the initiators, and not the receivers, of impulses and they, too, undergo trophic changes and even complete dedifferentiation, as in the case of the taste buds, upon denervation.[8] Recovery or restoration of the sensory organ soon follows reinnervation by regenerating axons.

2. *Morphogenetic influences.* Morphogenetic influences are evident in embryonic development. Complete differentiation and development of muscle require that the nerve supply reach the muscle and that a junction be established. It has been shown that the connection is what is required and not the impulses.

Morphogenetic influences are also evident in later stages of development. Hix[9,10] showed that the renal innervation somehow prepares the kidney for response to circulating growth factors. When a puppy is deprived of that preparation by denervation in the first few days of postnatal life, the development of the kidney is arrested. Morphogenetic influences of nerve are well reviewed by Gutmann[7] and Harris.[11]

3. *Role of nerve in regeneration.* Certain amphibia (newts) are capable of regenerating entire limbs and tails after amputation. Regeneration is prevented, however, by denervation of the stump. Only a portion of the fibers are required to sustain regeneration, and sensory fibers (which of course transmit impulses away from the limb tissues) serve this function entirely adequately. Experimental hyperinnervation of limbs (with nerves from other parts of the body) in species that ordinarily are incapable of regeneration has made possible a remarkable degree of regeneration—in the frog, in a species of lizard, and in the opossum, a primitive mammal.[12]

4. *Regulation of genic expression.* Red and white muscle (and other, intermediate types) are known to differ morphologically, functionally, and chemically. The chemical differences include those in proteins, enzymes, and metabolic pathways. Surgical section and cross-reinnervation of red and white muscles are followed by a high degree of cross-transformation, in a variety of species. This result means, in effect, that the nerve instructs the muscle what kind of muscle to be, and is an expression of a neurally mediated genetic influence. Apparently, the nerve that grows into a muscle in the course of embryonic development (and to which, ordinarily, it is joined for life) determines which of the genes of the muscle cell will be repressed and which will be expressed.*[6,7,13]

5. *Nerve-to-muscle transmission.* Another example, apparently, of genic expression and repression by neural influence occurs in junctional transmission from nerve to muscle. Receptor molecules for acetylcholine (ACh), which is released by nerve terminals, are normally restricted to the junctional area of the muscle surface. When the nerve is cut, however, the entire surface of the muscle cell may become ACh-sensitive due to removal of the repressive influence of the nerve on the synthesis of the (protein) receptor molecules in the extrajunctional areas.[14-16] That this continual repressive influence depends on "connectedness" and not impulses is demonstrated by experiments in which conduction in the (intact) nerve is chronically blocked by anesthetics. Under these circumstances of nerve-impulse deprivation, the electrodiagnostic parameters of the reversibly paralyzed muscles remain the same as in intact controls.

Reviews of other aspects of neurotrophic relations can be found in the literature.[6,7,12,18-20]

How trophic influences are exerted

Connections between nerve cell and muscle cell

In this paper inquiry on how trophic influences are exerted will be limited to the most familiar and best studied manifestation of neurotrophic influences;

*There is some evidence that part of this influence may be based on difference in impulse patterns. However, until this issue of impulse versus nonimpulse is resolved, this influence is logically included among the long term "trophic" functions of nerve.

namely, atrophy of denervation. Why does a muscle atrophy when its nerve is severed? When it is denervated, what has it been deprived of that is essential for its maintenance, for its regeneration, and for regulation of its functional and metabolic characteristics? As indicated before, the evidence is overwhelming that nerve impulses are not the essential elements. What does seem to be essential is intactness of connections between the nerve cell and the muscle cells it innervates. As long as protoplasmic continuity is maintained in the axons from perikaryon to motor endplate, even if it is nonconducting,[17] the neuronal trophic influence continues to be exerted. Indeed, trophic influences continue for a time after the perikaryon has been separated: The longer the stump attached to the muscle, the longer the time before postdenervation changes appear. This feature seems to indicate that what matters is the amount of nerve substance still available to the muscle, and that when it has been exhausted, trophic support ends.

Axonal transport

What causes the axon itself to undergo (wallerian) degeneration when protoplasmic continuity between it and the mother cell is interrupted? How does the axon distal to the interruption (even at a meter's distance, as in the human sciatic nerve) "know" that it has been separated? It has seemed to me that answers to these questions might offer some clues to trophic mechanisms. In this connection, it is important to compare neurons to other cells.

As in all cells, there is continual turnover, that is, degradation and replenishment of cytoplasmic components such as proteins, enzymes, nucleic acids, and such structural elements as mitochondria and ribosomes. These processes are under the nuclear DNA influence specific to the organism and the type of cell. In most cells, these nucleocytoplasmic interactions are carried on over distances measured in microns.

The nerve cell, especially the peripheral neuron, differs from other cells in that the largest part of the cytoplasm, instead of surrounding the nucleus, has been spun out into a long, slender thread. Hence, in the neuron, the interactions between cell body and the cytoplasm in the axon (the axoplasm) and the replacement of degraded components take place over distances measured not in microns but in centimeters, even in meters.

How is this accomplished? Reliance on diffusion would require impossibly long times. In the late 1940s Weiss and Hiscoe[21] showed continual streaming of axoplasm, from the cell body and along the entire length of the axon and all its branches. This axoplasmic flow appears to be the mechanism by which specific axonal components, substances and subcellular structures not supplied by the blood stream or by the Schwann cells, are continually replenished. The rate of flow was estimated at 1 mm./day.

In the intervening years, axonal transport, as the flow has come to be called, has been a very active area of investigation, and excellent reviews are available on the subject.[22-25] Among the components axonally transported are proteins, phospholipids, enzymes, glycoproteins, neurotransmitters and their precursors, mitochondria, and other organelles. Although rates of approximately 1 mm./day have been found to be common to many mammalian nerves, it is now known that there are several rates of transport, up to several hundred millimeters per day, different "cargoes" being carried at different rates. Also, different cellular mechanisms of transport seem to be involved, the motor power for which is provided by the axon itself. Transport continues for a while even in axons separated from their cell bodies, as in distal stumps left attached to muscle.

It should be mentioned in this connection that retrograde axonal transport—*toward* the cell body—also takes place. This retrograde transport seems to be the means by which the *cell body* "knows" that its axon has been severed, as reflected in the cellular changes associated with chromatolysis. Other aspects of retrograde transport will be mentioned in a later section.

Relation of axonal transport to trophic function

Is it possible that the trophic dependence of a muscle or other cell is, as for the axon, based on the continual delivery, *by the axon*, of substances that originate in the nerve cell? This was the question that occurred to me after the Weiss and Hiscoe report appeared in 1948. But it was not until the mid-1960s, when the necessary radioisotope technology and skills became available, that my coworkers and I were able to address the question experimentally.[26]

Our strategy was to:

(1) apply to the selected nerve cells isotope-labeled precursors (for example, amino acids) to be absorbed by them and incorporated into macromolecular substances (for example, protein); (2) trace the migration of the incorporated radioactivity along the axon; (3) determine how much crosses the junction and enters the muscle cells; and (4) rigorously exclude delivery by any other means, such as the blood stream, or measure it and correct for it.

The most difficult part of the strategy was control for nonaxonal delivery. The musculature and innervation of the tongue seemed to provide a system ideally suited to this study, especially to satisfying this requirement.

Minute volumes of radioactive precursor solutions were applied to the floor of the fourth ventricle in rabbits, under sterile conditions, and in such a manner as to minimize "washout" by cerebrospinal fluid from the area of the hypoglossal nucleus. The left hypoglossal nerve was sectioned in each animal. The animals were killed at various times after surgery, and the tongue and hypoglossal nerve removed. The distribution of radioactivity was studied in the nerve by scanning, and in histologic sections of the tongue, by autoradiography.

The following observations were made:

1. Radioactivity advanced along the nerve at about 5.5 mm./day and, as could be predicted from the average length of the nerve in our rabbits, began reaching the tongue on about the eighth postlabeling day. (Autoradiographs were prepared from rabbits killed on days 8 to 15).
2. Only the right (innervated) side was significantly labeled, the left (denervated) side showing only background activity.
3. Radioactivity appeared first at the base of the tongue and advanced over several days to the tip in accordance with the longer pathway to the tip.
4. Although the tongue comprised a variety of tissues (muscle, epithelium, blood vessels, glands and sensory apparatus, innervated by cranial nerves V, VII, IX, X, and XII, and by sympathetic fibers), *only* the muscles of the tongue were significantly radioactive.

Had delivery been by body fluids, (1) the entire tongue would have been instantaneously labeled; (2) both innervated and denervated sides would have been simultaneously labeled; (3) the labeling, base to tip, would have been instantaneous along the entire length, rather than sequential; (4) all components of the tongue would have been labeled; and not only muscle cells (as indeed happened when "washout" occurred or when precursor was injected intraperitoneally).

Radioactive particles were found within various parts of the muscle cells (nuclei, cross-striations and sarcoplasm) as well as in terminal nerve fibers and motor endplates. Furthermore, in a given microscopic field, it was often found that only *some* of the muscle cells were labeled—those whose innervating axons were visibly laden with radioactive particles. (Precursor apparently failed to reach many, perhaps the deeper-lying neurons, in the hypoglossal nucleus.)

These observations convinced us that between the eighth and fifteenth days after neuronal labeling, nerve-cell proteins reached the muscle cells, and that delivery was made by the axons. We proposed, in our first publication on the subject, that this intercellular transfer may be at the basis of neurotrophic function.[26]

Dynamics of nerve-to-muscle transfer

Having demonstrated cell-to-cell transfer of macromolecular substances, my coworkers and I turned to a quantitative study of the time-course of the delivery of proteins after synthesis in the neuron. For this purpose we extracted proteins from the hypoglossal nerve and styloglossus muscle of the tongue at various periods after applying tritiated leucine to the hypoglossal nucleus, and measuring, by liquid scintillation, the radioactivity incorporated in the proteins. The details can be found in our report.[27] Worth mentioning here, however, is our method for assaying, in tissue specimens from each animal, what portion of the radioactive protein represented incorporation of blood-borne radioactive leucine. We had previously shown, on sham-operated rabbits in which tritiated leucine had been intraperitoneally injected, that the mylohyoid and stylohyoid muscles, innervated by cranial nerves V and VII, respectively, incorporated the same amount of blood-borne leucine per milligram of tissue as the tongue muscles, and were therefore an ideal control. Hence, these muscles were removed from each experimental animal (in which the precursor had been applied to the hypoglossal nucleus), and analyzed for radioactive protein. They revealed, for each animal, what portion of the total protein-incorporated radioactivity in the tongue muscles was due to tritiated leucine taken up from the blood stream, the balance being radioactive protein delivered by the hypoglossal nerve.

We performed three experiments for each of the days between surgery and sacrifice of the rabbits for tissue specimens. In the first months of the research, we confirmed our autoradiographic demonstration of delivery between postsurgery days 8 and 15. Radioactivity well above background levels was present on day 8, rising to a peak at about day 12, after which it declined.

However, on extending our experiments, for many more months, into periods before the eighth day and after the fifteenth, we found waxing and waning of radioactive protein in the muscle, beginning as early as 6 hours (the shortest period tested) and continuing for more than a month. In contrast, the levels of radioactive protein in the control muscles (from blood-borne precursor) was much lower

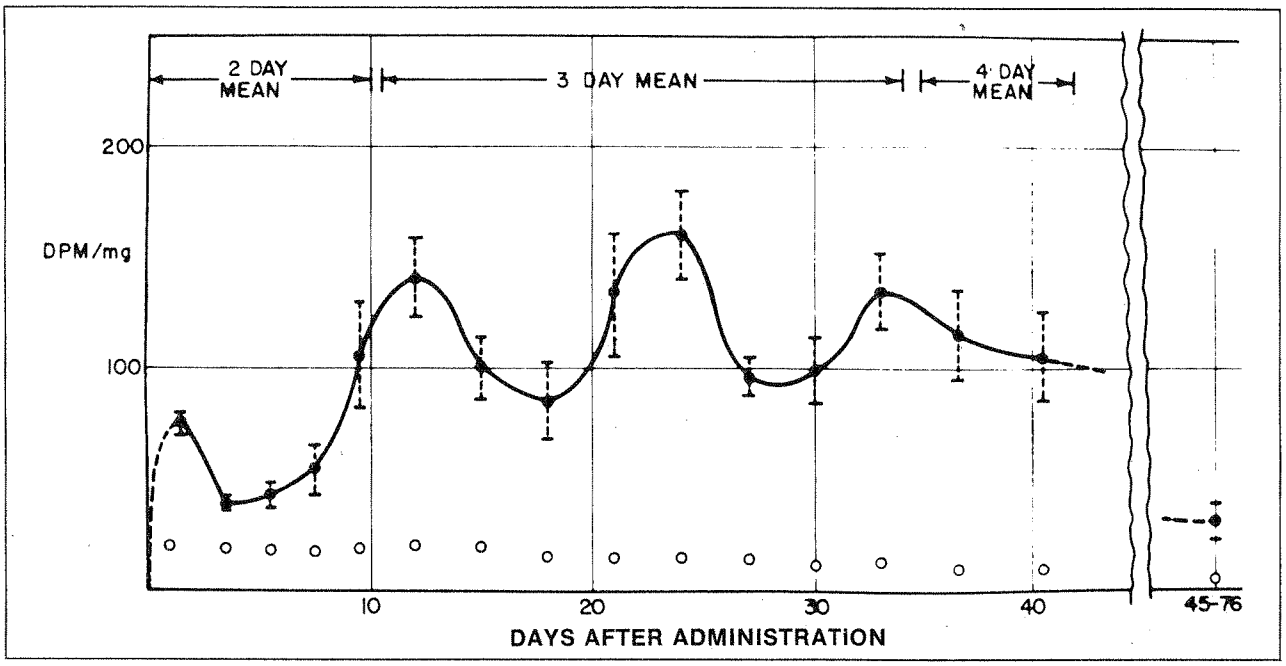

Fig. 1. *Waves of axonal transport of tritium-labeled nerve-cell proteins to muscle (hypoglossal nerve to styloglossus muscle). Closed circles: Total radioactive protein in disintegrations per minute per milligram. Open circles: Radioactive protein incorporating blood-borne precursor. Differences between open and closed circles indicate nerve-delivery radioactive protein.* (Reprinted with permission.)[27]

to begin with and declined steadily throughout. Depending on the fluctuating levels of total radioactive protein, the blood-borne portion varied from 10 to 40 percent of the total. The fluctuations, therefore, were in nerve-delivered protein, comprising most of the total radioactivity.

By appropriate statistical treatment of our data,[27] to compensate for variations in nerve length among different animals and for variations in actual dose of radioactive leucine, we showed four distinct waves of delivery of protein-incorporated radioactivity to the tongue muscle by the hypoglossal nerve (Fig. 1). This can be contrasted with the steady decline of the blood-borne component as represented by open circles in the illustration.) The first wave began within a few hours after precursor was applied to the neurons and reached a peak between the first and second days; the protein carried in this wave seemed to be metabolized and eliminated rapidly from the muscle. The second wave, which corresponded to that in our previous autoradiographic studies, peaked between days 9 and 14. A third peaked between days 22 and 27. A fourth wave was evident in the interval between days 30 and 35, after which protein radioactivity declined gradually. At day 76, however, it was still significantly above control levels (Fig. 1).

The troughs in protein radioactivity seem to represent overlap of the declining phase of one wave and the rising phase of the succeeding one. That is, during at least a part of each wave other than the first, protein radioactivity may represent the algebraic sum of overlapping waves and possibly include residues of preceding waves. Hence, during the years when many investigators of axonal transport were finding and confirming that there was not one rate, as had been thought, but multiple rates of movement of different proteins, varying from a fraction to several hundred millimeters per day, we were discovering multiple waves of arrival of neuronal proteins at the muscle.

These data show that at any given time, proteins carried in the hypoglossal axons are continually reaching the tongue muscle. Some of them had been synthesized by the perikaryon a few hours earlier, some about a month earlier, and the rest at two intermediate periods. These waves may be ascribed in part to different rates of axonal transport and in part to differences in departure time. (It is known that some proteins may remain in the cell body for as long as 2 weeks before being "exported.")

Protein composition in the four waves

The demonstration of multiple delivery waves raised a new set of questions: Are different proteins axonally transported and delivered in each of the periods? Can specific proteins be traced from

medulla, through the nerve, to the tongue muscle? Do all the protein fractions carried in the axon reach the muscle, or is there some selection? Are the proteins that are delivered to the muscle different from those synthesized by the muscle itself?

To approach these questions we undertook new investigations, which have yielded reasonably firm answers.[28,29] The new features were as follows: (1) Rabbits that had been prepared as in previous investigations were sacrificed for tissue specimens at *peak* times in each "wave," namely, days 1, 12, 22, and 34, to maximize the yields of radioactive protein. (2) The proteins extracted from the tissues were, first, divided by centrifugation into soluble and insoluble portions (the insoluble being those associated with particulate cellular elements), each of which was assayed for radioactivity. (3) A portion of the supernatant, that is, the soluble proteins, were fractionated by acrylamide gel disk electrophoresis, which yielded approximately forty fractions for radioassay, most of them common to all the tissue specimens. About a dozen of these were distinguished from the others by relatively high levels of radioactivity, and hence were easily identified and "tracked" from hypoglossal nucleus to nerve to tongue. (4) In the second of these studies,[29] additional fractions were obtained (with tritiated lysine as precursor) by chemical detachment of some "insoluble" proteins from the dense particles, rendering them soluble and subject to electrophoretic analysis. Still other, "basic" protein fractions (distinguished from the so-called acidic proteins of the previous study) were obtained by variation of pH and density of the acrylamide gels.

Following, in general terms, were our observations:

1. Of the 12 conspicuous "spikes" of soluble radioactive proteins evident in the medulla (hypoglossal nerve cells) on day 1, only 2-3 were evident in the nerve, the rest not appearing until day 12.

2. The proteins reaching the muscle in the first wave (day 1) were almost exclusively insoluble. (Investigators studying axonal transport had also generally agreed that insoluble or structural proteins are carried in the rapid transport system.)

3. With certain exceptions (to be discussed) electrophoretic fractions were traceable from hypoglossal neurons through nerve to muscle.

4. Each wave carried a different mixture of proteins, as observed in nerve and muscle, although there were fractions common to consecutive waves because of the overlap previously mentioned.

5. The transfer of radioactive proteins was not the same between adjacent nerve segments as it was between the distal segment of the nerve and the styloglossus muscle. Thus the proximal and distal segments of the nerve followed the same course with respect to ratios of soluble/insoluble protein activity, as would be expected of parts of the same compartment. However, in the transfer to muscle, insoluble proteins were favored in the first two waves (days 1 and 12), and soluble proteins in the later two waves (days 22 and 34). Similar discontinuity was evident with respect to the electrophoretically separated fractions. These fractions appeared and disappeared simultaneously in the proximal and distal segments of the nerve. In the course of transfer of radioactive proteins from distal segment to muscle, the entrance of some proteins into muscle was at the same intervals as that into nerve; the entrance of others was delayed to a later wave; and the entrance of still others into muscle never was apparent.

6. Proteins synthesized by the muscle (from blood-borne amino acids) were different from those delivered by the nerve.

The following conclusions may be drawn from these observations and from earlier studies:

1. Some proteins synthesized in the hypoglossal nerve cells are held for up to 12 days before being dispatched into axons.

2. Each of the four waves carries a different complement of proteins synthesized in the perikaryon, with some admixture due to overlap of the waves.

3. Although there is continuity of transport from one part of the nerve to the next, there is discontinuity of transfer from nerve to muscle.

4. Transfer of proteins from nerve to muscle is a different, apparently slower, process than transport along the nerve.

5. Transfer of proteins across the junction is selective, only *some* of the proteins being permitted to cross.

6. The neuron supplies proteins that are not manufactured by the muscle.

7. Hence, certain proteins synthesized in the nerve cell are specifically destined for muscle cells, the others for nerve, although some may be in common.

Thus, increased support and elaboration is gained for the hypothesis, that trophic influences of nerves on target organs depend, at least in substantial part, on the delivery of specific neuronal proteins by axonal transport and junctional transfer.

Since my coworkers and I first proposed this hypothesis in 1967,[26] evidence from other laboratories has accumulated that (1) proteins extracted from nerves exert trophic influences on nonneural cells; (2) that tropic influence depends on axonal transport; and (3) that proteins cross junctions between neurons and other cells. For

example, Oh and Markelonis[30] showed that the addition of a protein fraction extracted from the sciatic nerve to aneural cultures of embryonic and adult muscle cells arrests and reverses the decline of acetylcholinesterase that ordinarily occurs in such cultures and in denervated muscle. That is, the trophic regulation of this enzyme in muscle seems to be mediated by a protein of neural origin.

Others[14-16] have shown that blocking axonal transport with certain alkaloids, while leaving intact nerve conduction and the ability to maintain muscle activity, caused the appearance of trophic signs of denervation. Still others[31-33] have demonstrated the transsynaptic transfer of neuronal proteins.

Retrograde transport

As mentioned earlier, axonal transport is bidirectional. Transport from nerve ending to the cell bodies has been demonstrated in various ways by the following: (1) axonal swellings (accumulated axoplasm) that develop when two ligatures are applied to a nerve; (2) microcinematography, which shows organelles and particles in motion; (3) the migration of radioactive proteins in motor nerves when the muscles or other effectors have been injected with radioactive amino acids; (4) the similar transport of other tracer substances that are microscopically visualized by their color reactions (for example, horseradish peroxidase and ferritin); (5) the delivery, via axons, of neurotropic viruses and toxins from peripheral tissues to central neurons; and (6) observations on specific endogenous substances that are centripetally transported. The visual tracers have been used by neuroanatomists and others to trace unknown central pathways from the (known) sites of their terminals to their cellular origins in the central nervous system.

Retrograde transport seems to be a fundamental means of communication between neurons and between neurons and nonneuronal cells. It is presumed that one of the functions of retrograde transport is that of feedback (of unconsumed and undegraded axonal components), which would serve to regulate macromolecular synthesis in the perikaryon. Another apparent function is that of "informing" the perikaryon about circumstances in the periphery (that is, in other neurons or innervated nonneuronal cells). Two-way transport of specific substances with trophic influences may therefore have an important role in the maintenance of the plasticity of the nervous system. It would serve to keep motoneuron and muscle cell or two synapsing neurons mutually adapted to each other and responsive to each other's changing circumstances.

Still another role is the transport from the innervated structure to the neuron of specific substances that specifically regulate the function, metabolism, and development of the neurons and, possibly, their synaptic connections. A remarkable example of this is the transport of nerve growth factor, apparently from effectors innervated by sympathetic neurons to the ganglion cells, where it induces the formation of certain essential enzymes. It seems also to be essential for, and to have influences on, synapse between pre- and postganglionic neurons.[34]

Certain neurotropic toxins and viruses are known to reach the central nervous system or autonomic ganglia, where they exert their pathologic influences, by binding to peripheral nerve terminals and subsequent retrograde transport. An exciting aspect of this is the demonstration that tetanus toxin not only reaches the motoneuron or autonomic cell body, it also crosses the junction with presynaptic neurons.[35] The same is also true of a nontoxic fragment of tetanus toxin. Since that toxin binds other substances which it then carries with it, the possibility is opened that such carriers may one day be used to administer drug molecules to the central nervous system which are at present ineffective because they do not cross the blood-brain barrier.[34]

A more detailed discussion of retrograde transport is beyond the scope of this paper, which is primarily concerned with influences of neurons on innervated structures. It is included, however, because, like orthograde transport, it may also be expected to be vulnerable to biomechanical impairment, and it is likely to have additional clinical implications. The reader will find the review by Thoenen and associates[34] of great interest.

Clinical implications

It is clear that peripheral nerves not only conduct impulses to or from the nonneuronal cells and tissues that they innervate, but that they exert longterm influences on them that have their basis in mechanisms other than excitation and conduction. These influences, commonly identified as trophic or neurotrophic, are, as in the case of skeletal muscle and certain sensory organs, essential for their development, growth, and very survival. Other trophic influences are expressed in the control of structural and functional characteristics of innervated tissues. In some species, neurotrophic influences make possible the regeneration of entire extremities.

Conversely, it has been known for many years that the size, nature, special qualities, and other circumstances in the innervated tissue profoundly

influence the structural, functional, and metabolic properties of the innervating neurons.

It is now generally agreed that these "neuron-target cell interactions"[19] are inseparably related to the axonal transport of specific macromolecular substances. These substances, carried proximodistally, are elaborated by the cell body. Some of these in the original or modified form, return in the retrograde stream to the cell body along with other substances from the terminals or from innervated tissues.

Any factor that causes derangement of transport mechanisms in the axon or that chronically alters the quality or quantity of the axonally transported substances could cause the trophic influences to become detrimental. This alteration in turn would produce aberrations of structure, function, and metabolism, thereby contributing to dysfunction and disease.

Almost certainly to be included among these harmful factors are the deformations of nerves and roots, such as compression, stretching, angulation, and torsion, that are known to occur all too commonly in the human being, and that are likely to disturb the intraaxonal transport mechanisms, intraneural microcirculation, and the blood-nerve barrier.[23,36-40] Neural structures are especially vulnerable in their passage over highly mobile joints, through bony canals, intervertebral foramina; fascial layers, and tonically contracted muscles (for example, posterior rami of spinal nerves and spinal extensor muscles). Many of these biomechanically induced deformations are, of course, subject to manipulative amelioration and correction.

Another factor, also biomechanical in origin, is the sustained hyperactivity of peripheral neurons (sensory, motor, and autonomic) related to those portions of the spinal cord associated with intervertebral strain or other types of somatic dysfunction.[1] Sustained high rates of impulse-discharge place increased energy demands on the affected neurons, thus affecting their metabolism and almost certainly their synthesis and turnover of proteins and other macromolecules. Indeed, it has been demonstrated that such intense activity does impair axonal transport[41] and, one would expect, trophic interchange with other cells.

Hence, consideration of the neurologic impact on human health of postural and biomechanical defects in the body framework that are amenable to manipulative therapy should no longer be restricted to disturbances in impulse traffic. Although the consequences of disturbances in impulse traffic —pain and motor, sensory and autonomic dysfunction—are undeniably serious, the more subtle and insidious trophic consequences of disturbances in axoplasmic composition and transport are no less important. It seems likely that much of the efficacy of manipulative therapy is related to the amelioration of these trophic factors. The relationship between axonal transport and neurotrophic function and somatic dysfunction, therefore, merits much more clinical and investigative attention than it has been receiving.

In this connection it is important to acknowledge A.T. Still's prescient insight that "...the law of the freedom of the nutrient nervous system is equal if not superior in importance to the law of the free circulation of the blood"[42] and "that all diseases are mere effects, the cause being a partial or complete failure of the nerves to properly conduct the fluids of life."[43]

Appreciation is expressed to Mrs. Jane Denslow and Dr. Morris Thompson for bringing quotations from Andrew T. Still to my attention.

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Accepted for publication in December 1980. This paper is an adaptation of a lecture presented at an international Conference on Manipulative Therapy in the Management of Musculoskeletal Disorders, Lincoln Institute of Health Sciences, Melbourne, Australia, August 14-17, 1979. (Publication: Aspects of manipulative therapy, Melbourne, 1980.)

Dr. Korr is professor of medical education, Texas College of Osteopathic Medicine, Fort Worth, Texas.

Dr. Korr, NTSU/Texas College of Osteopathic Medicine, Camp Bowie at Montgomery, Fort Worth, Texas 76107.