Review Article

What is axoplasmic transport? Considering the role of exercise training: A mini review

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Abstract

Like other cells in the body, nerve cells need many proteins and substances to maintain homeostasis. As we know, the transcription and translation of proteins and necessary cellular substances occurs in the cell nucleus. The nucleus of nerve cell is located in the cell body. Another part of the nerve cell is “Axon”, which has a long structure. Even in some nerve cells axon’s length reaches up to 1000 mm. On the other hand, all parts of the neuron need substances and proteins synthesized in nucleus locating in the cell body. Therefore, a mechanism is necessary to express the movement of materials from nucleus along the axon. The movement of materials along the axon is called ‘Axoplasmic Transport’. It seems that disturbances in axoplasmic transport can cause various neuronal problems. The purpose of this study is to investigate the mechanism of axoplasmic transport and its types; moreover, the possible effect of exercise on this transition will be discussed.

Key Words: **Dynein, Kinesin, Motor proteins, Nerve terminals, Neurons**

Introduction

The human body is composed of trillions of cells. They provide structure for the body, take in nutrients from food, convert those nutrients into energy and carry out specialized functions. They are made up of different components and organelles without which our cells couldn't do their jobs and we would die. Like the furniture in your house, proteins wear out over time, so our cells are continuously making new proteins through the process of protein synthesis. Transcription and translation of proteins happens in nuclei (Dahlberg et al., 2003). In nerve cells the nuclei are located in the cell body which is the place for synthesis of different components and organelles. Another part of the nerve cell is the axon, which is often the longest processes emerging from neuronal cell bodies, known to extend up to several meters in length for vertebrate neurons (Vasudevan & Koushika, 2020). The polarized morphology of neurons necessitates the delivery of proteins synthesized in the soma along the length of the axon to distal synapses; critical for sustaining communication between neurons (Ganguly & Roy, 2022). This constitutive and dynamic process of protein transport along axons is termed "Axoplasmic (Axonal) Transport". Axonal transport is a critical energy demanding cellular process describing the movement of organelles, vesicles, and macromolecules toward (retrograde) or away from (anterograde) the soma (Mehta et al., 2022).

The earliest known experimental evidence for the existence of axonal transport comes from the seminal work in the sciatic nerve by Weiss and Hiscoe (1948), where axoplasmic material accumulated at sites of surgical constriction moved along the axon at a rate of ~1–2mm/day upon removal of the constriction (Weiss & Hiscoe, 1948). Subsequently, several studies examined the nature of axoplasmic transport, employing radioactive tracers to label proteins, lipids, and sterol content to monitor their flow through the axon (Vasudevan & Koushika, 2020). The active nerve cell synthesizes and releases neurotransmitters and growth factors; it also digests damaged and aged organelles by lysosomes and replaces them with newly synthesized organelles. The transfer of these materials,

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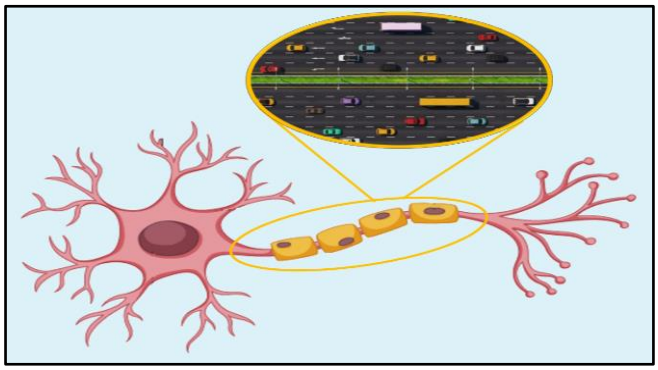

Figure 1. Axoplasmic transport

new organelles, lysosomes, vesicles containing neurotransmitters occurs entirely through the axoplasmic transfer mechanism. The active transport of organelles and other cargos along the axon is required to maintain neuronal health and function (Cason & Holzbaur, 2022). For this reason, it can be said that there is a direct relationship between the physiological activeness of neurons and the amount of axoplasmic transfer in them (Fig.1).

Axonal transport depends on some key components such as microtubules and motor proteins. Discovery of microtubules and motor proteins responsible for axoplasmic transport, has greatly improved the understanding of transport mechanisms employed by cells (Maday et al., 2014). Microtubules are long, thin structures that provide the roads along which cargoes are transported in all cells (Fig. 2). Several studies have demonstrated that microtubules can redistribute within growing neurons from the cell body into the axon and from the axon into the growth cone (Black, 2016). Motor proteins drive along microtubules to transport many passengers (Sleigh, 2020). Axonal transport can be classified based on the speed at which cargoes move (Gibbs et al., 2015). Radiolabeling experiments revealed two overall rate classes called fast and slow axonal transport (Roy, 2020), which will be discussed further.

Different speeds in axoplasmic transport

1. Slow axoplasmic transport

In this type of axoplasmic transport, substances move unidirectionally, only from the cell body to the axon terminal. This

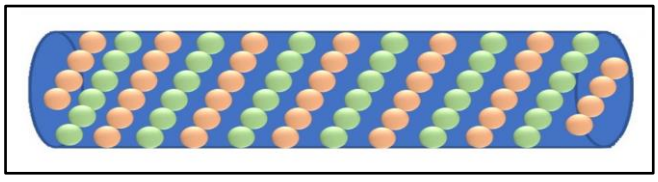

Figure 2. An image of microtubules

transport is called “Anterograde” (Guillaud et al., 2020). The mechanism of substance transport in this case includes transport by neurofilaments, microfilaments and microtubules. These three are cytoskeletal proteins that extend through the axoplasm and are used to transport materials. Neurofilaments are composed of three proteins: neurofilament L (NF-L), neurofilament H (NF-H) and neurofilament (NF-M) (Tsukita & Ishikawa, 1980). Microfilaments are composed of actin proteins (Carlson, 2019) and microtubules are composed of tubulin (α and β) (GM, 2000). Direct observations of individual microtubule or neurofilament segments indicated that they move down axons as assembled polymers (Brady et al., 2014). Studies suggest that cytoplasmic dynein may move microtubules with their plus ends leading and neurofilaments may move on their own or may hitchhike on microtubules (Brady et al., 2014). Slow axoplasmic transport has classifications according to the substances it transfers and the difference in transfer speed (Fig. 3). While the slowest group, termed ‘Slow Component a’ or SCa, was composed of the main cytoskeletal proteins, neurofilaments and microtubules; a slightly faster group within slow component carried cytosolic proteins and actin, termed ‘Slow Component b’ or SCb (Roy, 2020).

A. Slow Component a (SCa)

The speed of transmission in this type is 0.3 to 3 mm per day. The transfer substances are cytoskeleton polypeptides (tubulin, actin and neurofilaments). Spectrin and tau proteins can also be transferred by this mechanism (Brown, 2000).

B. Slow Component b (SCb)

The speed of transmission in this type is 2 to 8 mm per day. The transfer substances are soluble enzymes used in cellular metabolism (Caltrin, spectrin, calmodulin). Dynein, dynactin, glycolytic enzymes can also be transferred by this mechanism (Brown, 2000).

It has been argued that microtubule transport is important for establishing the microtubule polarity pattern of the axon, for the expansion of the axonal microtubule array during growth and development and its maintenance in the adults (Black, 2016). Impairment of microtubule transport in axons may also be a factor in neurodegenerative diseases by compromising the axonal microtubule array and thereby the various transport processes that depend upon it (Baas & Mozgova, 2012). Genetic evidence confirms an essential role for active transport in the neuron, as

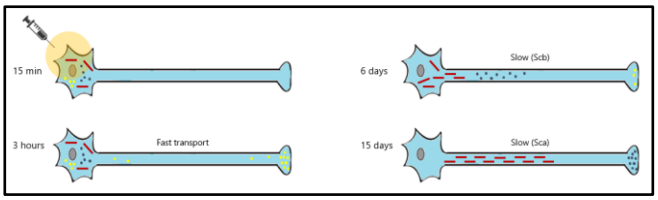

Figure 3. Tracking axoplasmic transport.

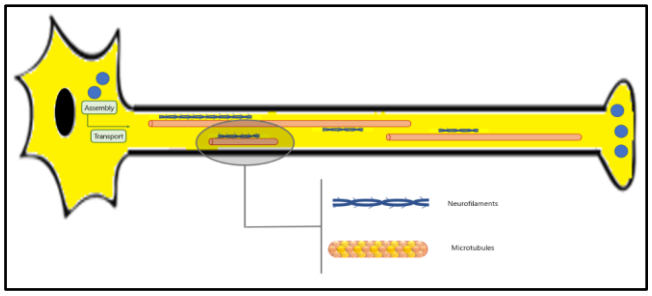

Figure 4. How substances move along the axon in slow axoplasmic transport

defects in many of the proteins involved are sufficient to cause either neurodevelopmental or neurodegenerative disease (Fig. 4) (Maday et al. 2014).

2. Fast axoplasmic transport

Fast motile structures resembling vesicles were seen in early microscopic studies (Grafstein & Forman, 1980). By development of transmitted light microscopy and video imaging in the 1980s, rapidly moving vesicles were unequivocally seen in extruded squid axons (Roy, 2014). With subsequent discovery of the motor protein kinesin (Brady, 1985; Vale, Schnapp, et al., 1985), it became obvious that the plethora of mobile vesicles was the visual correlate of "fast" radiolabel movement. In this type of transfer, materials move in two directions: the transport of materials from the cell body to the axon terminal (Anterograde) and the transport from the axon terminal to the cell body (Retrograde). The speed of this type of transfer is high and it's about 200 to 400 mm per day (Fig. 5) (Brown, 2000).

In the cell, small molecules, such as gases and glucose, diffuse to the place they are needed. Large molecules synthesized in the cell body as intracellular components such as vesicles and organelles such as mitochondria are too large (and the cytosol too crowded) to be able to diffuse to their destinations. Early biochemical and morphological studies established that material moving in fast axonal transport was associated with membrane-bound organelles. Mitochondria, membrane-associated receptors, synaptic vesicle proteins, neurotransmitters, and neuropeptides all move in fast anterograde transport (Brady et al., 2014). Motor proteins fulfill the role of transporting large cargo

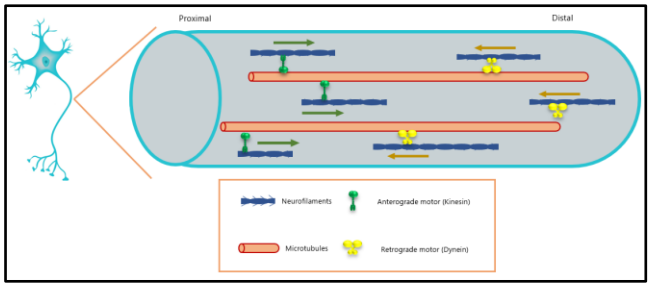

Figure 5. Fast axoplasmic transport pathway

from the cell to their required destinations. That's why this transport includes motor proteins that communicate with cytoskeleton. These motor proteins move on the cytoskeleton (microtubules) using energy (ATP) and carry the desired cargo. The type of motor protein differs according to the direction of material movement (forward or backward) (Woehlke & Schliwa, 2000). Materials transported in this type of transport include synaptic vesicles, different neurotransmitters, and different organelles (for example, lysosomes) (Brown, 2000). The group of fast-moving particles comprises membranous organelles such as Golgi-derived vesicles, mitochondria, endosomes and lysosomes among others (Cho et al., 2020).

A. Anterograde transport

This transport is done by a motor protein called kinesin (Fig. 6). This protein has a structure similar to the myosin motor protein and by consuming ATP, it transports cargo along the microtubule to the axon terminal (Morfini et al., 2012). Members of the kinesin superfamily vary in shape but the prototypical kinesin-1 motor consists of two Kinesin Heavy Chain (KHC) molecules which form a protein dimer (molecule pair) binding two light chains (KLCs), which are unique for different cargos (Vale et al., 1985). Kinesins are ATPases that walk towards the plus ends of microtubules in a hand-over-hand motion, with each motor head taking 16nm steps for every molecule of ATP hydrolyzed (Vasudevan & Koushika, 2020).

How does kinesin move?

Each head of kinesin molecule has two separate binding sites: one for the microtubule and the other for ATP. ATP binding and hydrolysis as well as ADP release changes conformation of microtubule-binding domains (Fig. 7).

B. Retrograde transport

Even though most axonal cargos are synthesized in soma, the concentration of many of these cargos is larger at the presynaptic terminal than that in soma. This requires transport of these cargos from soma to presynaptic terminal or other active sites in

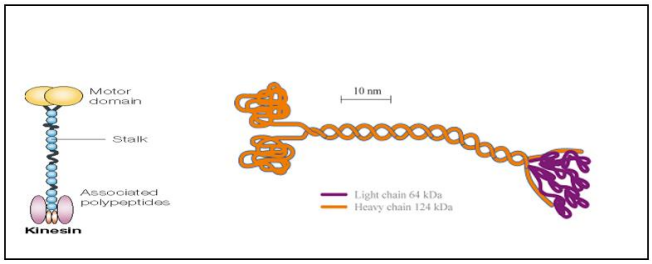

Figure 6. Kinesin Molecule

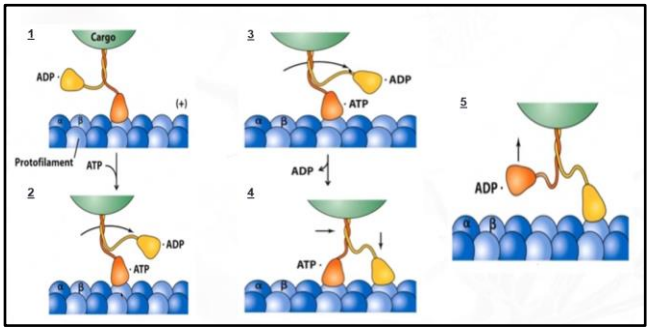

Figure 7. How kinesin molecule moves along microtubule: 1-A heavy chain of kinesin (tubulin binding domain) is attached to β-tubulin molecule while the other chain is located above. Also, cargo is attached to the light chain of the molecule (cargo binding domain). 2-ATP binds to tubulin-bounds heavy chain and provides the energy needed for a 180-degree rotation of free heavy chain of kinesin molecule. 3-The heavy chain that has moved forward is ready to connect β-tubulin. 4-ATP is broken and the heavy chain which moved forward, attaches to β-tubulin. 5-The first heavy chain is separated from tubulin and the movement continues in the same way.

axon (Kuznetsov & Kuznetsov, 2022). Retrograde communications from distal axons to cell bodies and/or dendrites play critical roles in the development and maintenance of neuronal circuits (Yamashita, 2019). Exogenous materials taken up in distal regions of axons may be moved back to the cell body by retrograde transport (Brady et al., 2014). This transport is carried out by a motor protein called dynein. This protein also has a structure similar to myosin and moves towards cell body along the microtubule by consuming ATP (Sickles et al., 2002). Cytoplasmic dynein, the major motor driving retrograde axonal transport, must be actively localized to axon terminals. This localization is critical as dynein powers essential retrograde trafficking events are required for neuronal survival, such as neurotrophic signaling (Twelvetrees et al., 2016).

This motor protein is only responsible for movement along the microtubule and cannot bind to cargo. Another protein called dynactin can bind to the cargo (Duncan & Goldstein, 2006). Then dynactin binds to dynein and transports the dynein protein and cargo like a tow truck (Fig. 8).

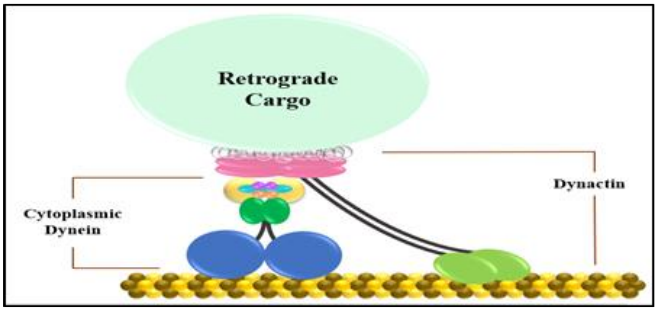

Figure 8. Dynein and dynactin

How does dynein move?

Dynein is a family of cytoskeletal motor proteins that move along microtubules in cells. They convert the chemical energy stored in ATP to mechanical work. As we mentioned before, dynein should bind to a protein complex called dynactin; otherwise, it won't be able to carry the cargo (Fig. 9).

In neurotrophin signaling, the retrograde axonal transport of endosomes containing active ligand-receptor complexes from distal axons to somatodendrite compartments mediates retrograde signaling. Therefore, the coupling between anterograde and retrograde axonal transport via signaling endosomes plays a critical role in regulating proper neuronal network formation (Yamashita, 2019).

Axoplasmic transport overview

A summary of the types of axoplasmic transport is reported in Table 1 (Brown, 2000)

Can exercise regulate axoplasmic transport?

Exercise can activate various cell signaling pathways. One of these pathways is the activation of adenylate cyclase. This enzyme facilitates converting ATP into signaling molecule "cAMP". The motor protein kinesin can be directly phosphorylated by cAMP-dependent kinase and binds to synaptic vesicles (Tao et al., 1999). Exercise also increases the amouant of available ATP during energy production processes. Metabolic changes induced by alterations in concentration of intracellular ATP may regulate axoplasmic transport as well because kinesin and dynein are ATPases that use ATP as their energy sources to transport vesicles (Tao et al., 1999). Increase in circulating fatty

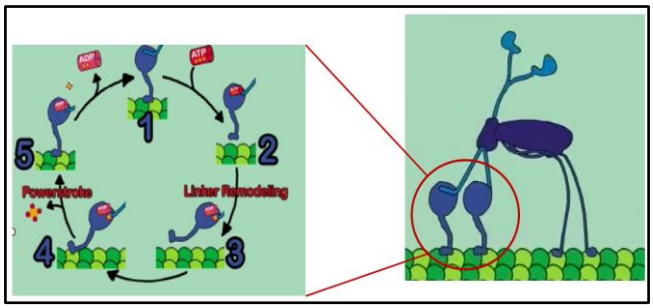

Figure 9. How the dynein molecule moves along the microtubule: 1-As the first step in mechano-chemical cycle of dynein, ATP binds to dynein and induces the required force to separate dynein from microtubule. 2-Remodeling of linker extends the search range of microtubule binding domain along the microtubule. 3-After hydrolysis of ATP to ADP and inorganic phosphate, the motor domain is sought to engage in new binding site on microtubule. 4-Strong binding to microtubule accelerates release of phosphate and induces linkers to revert to its straight form (power stroke). 5-Finally ADP is released from dynein's head and the cycle restarts.

Table 1. The moving structures of axonal transport

Rate class	Average rate	Moving structures	Composition (Selected examples)
Slow components			
Slow component 'a'	0.3–3 mm day–1	Neurofilaments microtubules	Neurofilament proteins tubulin, spectrin, tau proteins
Slow component 'b	2–8 mm day–1	Microfilaments, Supramolecular complexes of the cytosolic matrix	Actin, clathrin, dynein, dynactin, glycolytic enzymes
Fast components			
Fast anterograde	200–400 mm day–1	Golgi-derived vesicles and tubules (secretory pathway)	Synaptic vesicle proteins, kinesin, enzymes of neurotransmitter metabolism
Fast retrograde	200–400 mm day–1	Endosomes, lysosomes (endocytic pathway)	Internalized membrane receptors, neurotrophins, active lysosomal hydrolases

acids can also affect axoplasmic transport. A variety of fatty acids increase axoplasmic transport by supplying energy through β-oxidation pathway and citrate cycle (Takenaka et al., 2003). The release of neurotransmitters and hormones can also be affected by exercise. It has been reported that neurotransmitters and hormones can control the function of nervous system. BDNF has been implicated in axonal transport and a self-amplifying positive feedback mechanism mediated through cyclic adenosine 5′-monophosphate (cAMP), protein kinase A (PKA) and phosphatidylinositol 3-kinase (PI3 kinase) pathways to trigger further BDNF secretion, promote TrkB membrane insertion and stimulate anterograde axonal transport, thereby contributing to axonal development and formation of neuronal polarity (Khatib et al., 2021). Simultaneous overexpression of BDNF and TrkB enhances axonal transport in two neurodegenerative disease models: a humanized tauopathy model of Alzheimer's disease and an experimental glaucoma model (Khatib et al., 2021). It seems like adrenaline increases (Takenaka et al., 1994) and acetylcholine decreases (Takenaka et al., 1992) the number of transported particles and velocities in a mouse superior cervical ganglion (SCG) cells. Moreover, glucagon increases the number of particles undergoing axoplasmic transport in SCG cells and increases the velocity of axoplasmic transport (Tao et al., 1999).

Irisin can also be a proposed effector of exercise which may contribute to supporting nerve structure and improving the axonal transport through overexpression of structural proteins and their related regulatory proteins (Momenzadeh et al., 2021). Jasmin et. al. (1988) concluded that fast axonal transport of acetylcholinesterase in rat sciatic motoneurons is enhanced following prolonged daily running, but not following swimming. In other investigation they showed chronic endurance running induces significant adaptations in the fast axonal transport of labeled proteins (Jasmin et al., 1988). Gharakhanlou et al. (1999) demonstrated that the amount of CGRP anterogradely transported along axons by fast transport increased in sciatic motoneurons of exercise-trained rats.

Investigations on the effect of endurance exercise training on kinesin-5 and dynein motor proteins in sciatic nerves of male wistar rats with diabetic showed that endurance exercise as a non-medication strategy can moderate the upregulation of Kinesin-5 and Dynein motor proteins in diabetic rats (Golbar et al., 2018). Exercise increases neuronal activity leading to changes at the nerve terminal. Consequently, axonal transport of proteins increases in order to compensate for the effects exercise has on distal parts of motoneurons, thus allowing repair and return to normal nerve function (Farmer, 2010). Voluntary exercise increased axonal transport in exercised diabetic group, particularly in an anterograde direction (Farmer, 2010). Increased level of neurotransmitter NO and axonal transport may improve the signal transferring and synapse plasticity and result in the improvement of nerve function (Momenzadeh et al., 2021). Singleton et al. (2021) have also mentioned that exercise reverses hyperglycemia and consequent oxidative stress improves microvascular vasoreactivity, enhances axonal transp-

-ort, ameliorates the lipotoxicity and inflammatory effects of hyperlipidemia and obesity, supports neuronal survival and regeneration following injury, and enhances mitochondrial bioenergetics at the distal axon.

Discussion

The human body is made up of different cells. Different proteins and substances are synthesized daily in these cells. Cells have many features in common, but each type of them also possesses a functional architecture related to its unique physiology. Neurons are polarized cells, specialized for synthesizing membranes and proteins and conducting nerve impulses. In general, neurons have a cell body, a dendritic arborization that is usually located near the cell body and an extended axon that may branch considerably before terminating to form synapses with other neurons (Brady et al., 2014). These slender cylindrical processes can extend for distances in excess of one meter in large animals, yet they are dependent on the cell body for the synthesis of many of their components (Brown, 2003). Axoplasmic transport is the process of delivering proteins and other substances synthesized in the cell body of neuron to axon and axon terminals. It is a highly complex process essential for sustaining proper neuronal functioning.

In 1980, Raymond Lasek published an article on axonal transport entitled “Axonal Transport: A Dynamic View of Neuronal Structures” emphasizing the importance of axonal transport in the fine structure of the axon (Lasek, 1980). A large number of investigations have shown axonal transport defects and the role they play in motor neuron diseases (Beijer et al., 2019; De Vos & Hafezparast, 2017; Guo et al., 2020; Prior et al., 2017). Understanding the mechanisms by which long-range signaling occur in neurons is important to our knowledge of neuronal development, survival, and repair.

We overviewed cytoskeletal components and molecular motors involved in axonal transport mechanisms. Considering their speed, axoplasmic transport can be categorized in two types of slow and fast, each of which has its own specific character and mechanism. Slow axoplasmic transport is unidirectional transport from cell body to axon terminal. It can be categorized into two types: SCa and SCb. The other type of axoplasmic transport is fast. Efforts have focused on identifying the adaptor proteins that specify motor-cargo selectivity and the regulatory mechanisms that govern the directed transport of cargo-carrying opposing motor proteins (Guedes-Dias & Holzbaur, 2019). The difference between anterograde and retrograde fast transport is in motor protein responsible for this action. Kinesins are ATPases that walk towards the plus ends of microtubules in a hand-over-hand motion (Vasudevan & Koushika, 2020). Dynein is a family of cytoskeletal motor proteins that move retrogradely on microtubu-ules in cells. These motor proteins have a structure similar to the myosin motor protein and transport cargo along the microtubule by consuming ATP.

Exercise has been shown in different studies to cause changes in various cell signaling pathways. Results of different investigations have shown that exercise can affect release of neurotransmitters and hormones and these changes can affect axonal transport. For example BDNF (Khatib et al., 2021), adrenaline (Takenaka et al., 1994), acetylcholine (Takenaka et al., 1992),Glucagon (Tao et al., 1999) and irisin (Momenzadeh et al., 2021) can regulate axonal transport. Exercise shows effects on moderation of motor proteins activity (Golbar et al., 2018) and increasing axonal transport (Farmer, 2010; Gharakhanlou et al., 1999). Exercise can also support neuronal survival and regeneration (Momenzadeh et al., 2021; Singleton et al., 2022).

Conclusion

Axoplasmic transport is one of the main mechanisms in survival and physiological activities of neurons. Both the proteins synthesized in the cell body which move anterogradely and neurotransmitters and various substances in the terminal that move retrogradely are carried along the axon through this mechanism. Any disturbance in axoplasmic transport can cause various motor neuron disease. In this article, axoplasmic transport was explained and the mechanism of its types was reviewed. Also, some examples of how exercise has a positive effect on regulating axoplasmic transport are provided. However, detailed knowledge is not available on the effect of exercise on axoplasmic transport. What is clear is that exercise can stimulate different signaling pathways that facilitate axoplasmic transport but further investigations are needed.

What is already known on this subject?

It seems that disturbances in axoplasmic transport can cause various neuronal problems.

What this study adds?

Some examples of how exercise has a positive effect on regulating axoplasmic transport are provided.

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Compliance with ethical standards

Conflict of interest The author declare that she has no conflict of interest.

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Author contributions

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