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Impairment of Axonal Transport in Diabetes: Focus on the Putative Mechanisms Underlying Peripheral and Central Neuropathies

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Abstract

Diabetes mellitus is a chronic disease with numerous complications that severely impact on the quality of life of patients. Different neuropathies may arise as complications associated with the nervous system, both peripherally and at the central level. The mechanisms behind these neuronal complications are far from being clarified, but axonal transport impairment, a vital process for neuronal physiology, has been described in the context of experimental diabetes. Alterations in neuronal cytoskeleton and motor proteins, deficits in ATP supply or neuroinflammation, as processes that disturb the effective transport of cargoes along the axon, were reported as putative causes of axonal impairment, ultimately leading to axonal degeneration. The main goal of the present review is to reunite the main studies in the literature exploring diabetes-induced alterations likely involved in axonal transport deficits, and call the attention for the uttermost importance of further exploring the field. Understanding the mechanisms underlying neuronal deficits in diabetes is crucial for the development of new therapeutic strategies to prevent neuronal degeneration in diabetes and related neuropathies.

Keywords Diabetes · Axonal transport · Cytoskeleton · Kinesin · Dynein · Neurodegeneration

Abbreviations

AD	Alzheimer's disease
ATP	Adenosine triphosphate
CNS	Central nervous system
DRG	Dorsal root ganglion
KIF	Kinesin superfamily protein
NF	Neurofilament
NGF	Nerve growth factor
NT-3	Neurotrophin-3
PNS	Peripheral nervous system
TNF	Tumor necrosis factor
RGC	Retinal ganglion cell
SC	Superior colliculus
STZ	Streptozotocin

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Introduction

In diabetes, elevated glucose levels remain circulating in the bloodstream, leading to an inadequate glucose cell supply. Extracellular levels of glucose govern its neuronal uptake, and persistent episodes of hyperglycemia may lead to neuronal dysfunction, namely, by impairing the axonal transport [1].

Axonal transport is crucial to maintain neuronal homeostasis, being the fundamental communication route between the soma and synaptic compartments. The synapse is supplied by axonal transport with proteins and lipids synthesized in the cell body, which are essential for neurotransmission. Mitochondria are also transported along axons to supply local energy, and aggregated or misfolded proteins are cleared from the distal synapse to be degraded in the soma. Additionally, axonal transport allows the adequate neuronal response to distal trophic and stress signals [2]. Thus, any defect with impact in this hub can lead to cellular dysfunction and degeneration.

Herein, we review the current state of knowledge regarding axonal transport impairment in diabetes, focusing on several components of transport machinery and the mechanisms that control axonal transport at the peripheral and central nervous systems (PNS and CNS, respectively).

Axonal Cytoskeleton Changes in Diabetes

Axonal transport takes place along the cellular cytoskeleton, which is composed by three major components: actin filaments, neurofilaments (NF), and microtubules. Although all cytoskeleton components are important for neuronal morphology and function, axonal transport depends almost completely on microtubules and their associated motor proteins: kinesins and dyneins (Fig. 1).

Microtubules are the main cytoskeleton component and, in the axon, are oriented with their minus ends (α-tubulin) nearer to the soma and plus ends (β-tubulin) closer to the nerve terminal, conferring polarity to the axon [3]. This polarity directs motor proteins to undergo anterograde (towards the plus end) or retrograde (towards the minus end) transport [4].

In diabetic neuropathy, decreases in axon caliber, impairments in axonal transport and reduced capacity of nerve regeneration, support the existence of alterations in the integrity of the axonal cytoskeleton [5–7] (Fig. 2). In fact, a decrease in α-tubulin messenger RNA (mRNA) after 8 weeks of diabetes was reported [8], and an increase in the glycation of nonenzymatic tubulin in the sciatic nerve after 2 weeks of streptozotocin (STZ)-induced diabetes [9]. The glycation of brain tubulin has been also described in early experimental diabetes, subsequently affecting its ability to form microtubules [10]. In the sural nerves of diabetic patients, an increase in advanced glycation of cytoskeletal proteins and an increase in protein cross-linkage was detected [11], potentially causing axonal degeneration. In experimental diabetes, the hyperphosphorylation of the microtubule-associated protein tau was reported in the hippocampus [12], as well as an increase in the proteolytic cleavage of tau [13]. Tau modifications impair axonal transport through microtubule derangement, blocking the axonal trafficking route, which can culminate in synaptic dysfunction and consequent neurodegeneration [14].

Besides microtubule changes, abnormal NF expression, processing, and structure may contribute to diabetic neuropathy, since reduced synthesis of NF proteins or formation of incorrectly associated NF could severely disrupt the axonal cytoskeleton [15]. In fact, NF mRNAs are selectively reduced in diabetic rats and alterations on post-translational modifications of NF proteins have been detected [6, 8, 9, 16]. Abnormal NF phosphorylation has been described in sensory neurons and in the spinal cord of diabetic animals [17, 18], which may lead to progressive deficits of axonal function [19]. Additionally, alterations on the expression of several NF-associated protein kinases may also contribute to diabetes-induced changes on axonal transport [7].

Regarding the thinnest filaments of the cytoskeleton, the microfilaments, or actin filaments, which provide stability and allow the proper neuronal dynamics [20, 21], diabetes was reported to induce actin glycation in the brain of STZ-induced diabetic rats [9, 22].

Taken together, these studies in experimental diabetes indicate that altered expression of cytoskeletal components and post-translational modifications may interfere with cytoskeletal assembly, contributing to changes in axonal transport and consequently to nerve dysfunction.

Axonal Transport Impairments in the Peripheral Nervous System

Studies regarding transport rates along sciatic nerves of STZ-induced diabetic rats suggest an impairment of the retrograde axonal transport as the first event leading to neuronal dysfunction in diabetes, followed by an impairment of the anterograde axonal transport of structural proteins [23]. In short-term experimental diabetes, impairments in the anterograde and retrograde axonal transport of a phosphofructokinase were detected, validating the hypothesis that axonal transport impairment is an early event in diabetes, this effect being prevented by insulin treatment [24]. Accordingly, it was already reported more than three decades ago that diabetes leads to a decrease in the axonal transport of isotopically labeled glycoproteins and proteins in several types of peripheral nerves [25, 26]. In the sciatic nerve, after 4 weeks of diabetes, fast retrograde axonal transport is impaired and the transport and synthesis of proteins and glycoconjugates is compromised, which may be correlated with the early decrease in axon caliber and conduction velocity in peripheral nerves [26] (Fig. 2). Interestingly, the alterations in the fast axonal transport rates in the sciatic nerve are ameliorated by insulin administration [25], indicating that the regulation of glycemic levels may be effective not only in preventing alterations in the axonal transport but also in reverting them. Additionally, by using manganese-enhanced magnetic resonance imaging (MEMRI), which allows assessing in vivo axonal transport rates as manganese is transported along axons by microtubule-dependent axonal transport [27], it was demonstrated that hyperglycemia attenuates the rate of axonal transport in mice olfactory receptor neurons via activation of p38 MAPK-tau signaling cascades by oxidative stress [28]. Besides the alterations in axon caliber and in conduction velocity, nerve regeneration [29, 30] is also affected in diabetes, probably also due to the impairment in retrograde signaling from the injury site and growth factor supply [31]. In fact, diabetes induces changes in the axonal transport of distal trophic factors to the soma, such as nerve growth factor (NGF). The decrease in NGF expression in animal models of diabetes leads to deficits in its retrograde transport, resulting in an impaired support of NGF-dependent sensory neurons [32]. A decrease in the NGF transport induced by diabetes was also detected in the sciatic nerve [31] and in the cervical vagus nerve. In the latter, neurotrophin-3 (NT-3) transport was also affected [33]. The reduction of neurotrophic input due to diabetes-induced axonal transport alterations may lead to an impaired supply of

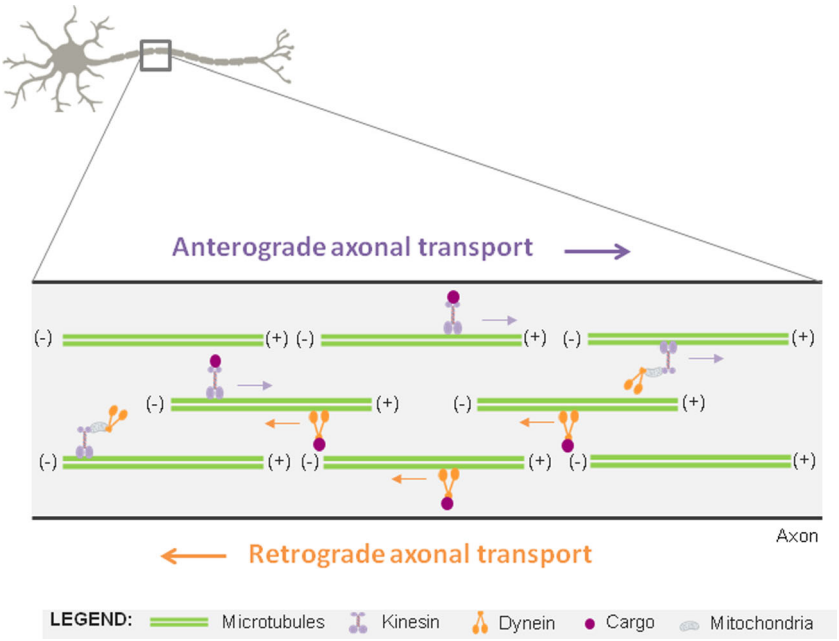

Fig. 1 Motor proteins involved in axonal transport. Microtubules are oriented with the plus ends in the direction of the synapse, and the minus ends towards the cell body, conferring polarity to the axon. Most axonal transport occurs along the microtubules, and is carried out by two groups of motor proteins that move in opposite directions: kinesins and dyneins. The specificity of these proteins movement allows the retrograde or anterograde transport of cargoes along the axon

neurotrophic survival signals [34]. Consequently, neurotrophin signaling changes may contribute to synaptic dysfunction and neurodegeneration.

Axonal transport deficits may be due to impairments in motor proteins [35]. Long-range intracellular transport is carried out by kinesins and dyneins that move along the microtubules in an adenosine triphosphate (ATP)-dependent manner. These motors recognize the polarity of microtubules: whereas most kinesin-family (KIF) motors move towards the plus end of microtubules and usually deliver newly synthetized components from the cell body to the synapse, dynein moves degradative components and survival signaling towards the cell body [4] (Fig. 1).

Alterations in motor protein content and distribution have been reported in experimental diabetes. In STZ-induced diabetic rats, KIF5B content is increased in the sciatic nerve, as well as KIF5B mRNA levels in spinal cord sensory and motor neurons [36]. Very recently, it was also demonstrated that diabetes increases KIF5B mRNA expression in male dorsal root ganglion (DRG) neurons of diabetic rats, whereas KIF5A protein levels were significantly decreased [37]. Additionally, KIF1A mRNA and protein levels were reported to be

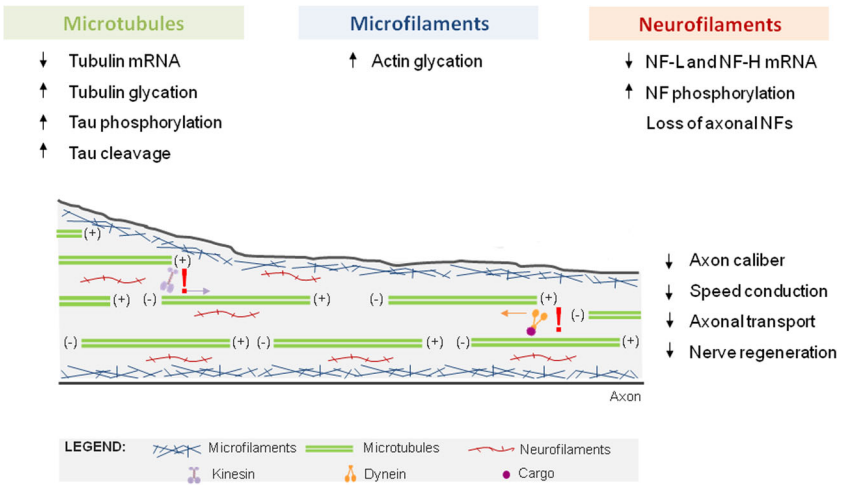

Fig. 2 Main alterations induced by diabetes in axons and cytoskeleton components reported in animal models of diabetes. Several alterations were reported in diabetes, mainly related to microtubules, which are the main route for axonal transport. Diabetic axons present an increased number of microtubules and neurofilaments proximally, as well as increased cross-sectional area near the cell body. On the other hand, axonal cross-sectional area near the synapse is decreased, and the number of microtubules and neurofilaments are reduced distally. As a consequence of cytoskeleton and nerve terminal derangements, motor proteins fail to bind microtubule end, contributing for the impairment of axonal transport

significantly increased in the DRG neurons of diabetic rats [37]. Taking into account that KIF1A motor has been shown to play a fundamental role in sensory neuron survival and function [38], any changes in this motor protein may contribute for the development of diabetic neuropathy.

Due to the observation that the velocity of anterograde and retrograde transport of mitochondria is decreased in neuronal cultures of KIF5A$^{-/-}$ knockout mice, KIF5A motors were associated to mitochondrial transport [39]. The majority of mitochondria are produced in the neuronal soma and then transported along microtubules to reach areas with high ATP demands, such as the synapse [4]. Generally, kinesin motor proteins carry out anterograde mitochondrial transport, while dyneins retrogradely transport them, being simultaneously coupled to oppositely directed molecular motors [4] (Fig. 1).

Considering the alterations previously described in KIF5 proteins induced by diabetes, it is likely that mitochondrial transport is affected by this pathology. Indeed, nerve degeneration in diabetes was already associated to alterations in the mitochondrial ultrastructure and physiology, and to alterations in mitochondrial trafficking in the PNS [40]. Very recently, it was reported that diabetes induces several alterations in the expression of proteins involved in mitochondrial function and dynamics at DRG neurons of STZ-induced diabetic rats [37]. Interestingly, a study on mitochondrial motility in DRG neurons showed that the exposure to elevated glucose levels did not reduce the percentage of motile mitochondria [41]. Since diabetes is a multifactorial pathology, it cannot be excluded that the alterations in mitochondrial transport may be caused by other factors besides hyperglycemia. In fact, a recent study demonstrated that palmitate, a free fatty acid involved in dyslipidemia in type 2 diabetes, induces DRG neuron mitochondrial depolarization, inhibiting their trafficking in the axons [42].

Hypoglycemia, a common condition affecting diabetic patients treated with insulin or other hypoglycemic drugs, may also affect the PNS [43, 44], impacting axonal transport [45]. In experimental studies, insulin-induced hypoglycemia leads to acute axonal degeneration in nondiabetic rats [46]. PNS appears to be quite vulnerable to low blood glucose levels during insulin-induced hypoglycemia [44], and motor axons seem to be more vulnerable than sensory axons to hypoglycemia [43]. Axonal transport was studied in nondiabetic and STZ-induced diabetic rats during acute and prolonged insulin-induced hypoglycemia. In nondiabetic animals, acute severe hypoglycemia decreased the amount of the anterograde fast component comparing to controls, being transport velocity unaffected. On the other hand, prolonged hypoglycemia prevented the decrease in the anterograde fast component, showing that axonal transport was more impaired under severe hypoglycemic conditions comparing to moderate hypoglycemia [45]. In STZ-induced diabetic rats, acute severe hypoglycemia produced a similar but less-pronounced decrease of the anterograde fast component [45]. These studies point forward that hypoglycemia is associated with alterations in axonal transport and may play a role in the development of neuropathy.

Additionally, it has been suggested that inflammation-induced axonal transport disruption may cause some symptoms of neuropathic pain [47]. Reduced axonal transport causes distal mechanical hypersensitivity consistent with neuropathic pain [48]. By disrupting axonal transport along a peripheral nerve by the local application of vinblastine, axonal mechanical sensitivity develops. It was also demonstrated that neuritis disrupts anterograde axonal transport [49]. These studies further emphasize the importance of axonal transport in the maintenance of axonal sensitivity and the role of its disruption in clinical pain mechanisms.

Axonal Transport Impairments in the Central Nervous System

Although most studies regarding diabetes-induced alterations in axonal transport were focused in the PNS, evidences from the brain, spinal cord, optic nerve, and retina indicate that axonal transport is also impaired in the CNS (Table 1). Indeed, an impairment in the axonal transport of NF subunits, tubulin and actin in the rat optic pathway, was reported [6, 57].

In the retina, diabetes induces a decrease in both slow and fast axonal transport with a simultaneous decrease in fast axonal transport and protein synthesis, whereas protein degradation remains unchanged [50, 51]. Studies using fluoro-gold, a neuronal retrograde tracer, demonstrated a decreased accumulation of this tracer in RGCs of STZ-induced diabetic rats, suggesting that retrograde axonal transport from the dorsal lateral geniculate nucleus in the brain to the RGCs in the retina is impaired [52]. However, in a type II diabetes animal model with obesity, retrograde axonal transport is not significantly decreased compared with control rats, suggesting that the axonal transport in RGCs is differentially affected in type 1 and type 2 diabetes [58]. Changes in the polyol pathway that result from metabolic changes associated with diabetes might play a role in the gradual impairment of retrograde axonal transport in the optic nerve of diabetic rats [53]. Besides changes in retrograde transport, an impairment in anterograde transport in RGCs (from the retina to the superior colliculus) in diabetic animals was also reported, indicating that the impact occurs not only in the retrograde transport but also in the anterograde transport [54].

Similarly to what is described in the PNS, motor proteins are also affected by diabetes in the CNS. In the retina, KIF1A motor protein immunoreactivity decreases in all retinal layers, excepting the outer and inner segments of photoreceptor layer and outer nuclear layer after 8 weeks of STZ-induced diabetes. KIF5B immunoreactivity was also altered, being increased in the outer and inner segments of photoreceptor layer and outer nuclear layer, and decreased in the inner plexiform and

Table 1 Diabetes-induced alterations in axonal transport in the CNS

Tissue/pathway	Animal model	Duration of diabetes	Transport mpairment	Cytoskeleton/cargo/ motor changes	Reference
Optic pathway	Alloxan-induced diabetes (rabbits)	1 week	Reduced retinal protein biosynthesis and reduced fast and slow axonal transport	_	Chihara et al. [50]
Optic pathway	STZ-induced diabetes (rats)	4–6 weeks	Impaired cytoskeleton protein transport	NF subunits, tubulin, and actin	Medori et al. [6]
Optic pathway	Alloxan-induced diabetes (rabbits)	1 week and 3 and 7 months	Reduction and change in spectrum of fast axonally transported proteins	_	Tsukada and Chihara [51]
Optic pathway	Biobreeding rats	2.5–3.5 months	Impaired cytoskeleton protein transport	NF subunits, tubulin, and actin	Medori et al. [20]
Brain and spinal cord	STZ-induced diabetes (rats)	6 weeks	_	Increased brain actin glycation and phosphorylation of spinal cord NF proteins	McLean et al. [9]
DGN to RGCs	STZ-induced diabetes (rats)	3 months	Impaired retrograde axonal transport	_	Zhang et al. [52]
DGN to RGCs	STZ-induced diabetes (rats)	1 and 3 months	Impaired retrograde axonal transport	_	Ino-Ue et al. [53]
RGCs to SC	STZ-induced diabetes (rats)	6 weeks	Impaired anterograde axonal transport	_	Fernandez et al. [54]
Hippocampus	STZ-induced diabetes (rats)	8 weeks	_	Increased expression and content of KIF1A and KIF5B	Baptista et al. [55]
Retina	STZ-induced diabetes (rats)	8 weeks	_	Changes in KIF1A, KIF5B, and dynein content and/or distribution	Baptista et al. [56]

ganglion cell layers. Regarding dynein, no significant changes were detected in the retina, with the exception of increased immunoreactivity in ganglion cell layer [56]. The increase in dynein immunoreactivity may be a consequence of changes in microtubules leading to an accumulation of dynein at the soma of retinal ganglion cells (RGCs). Alternatively, dynein may be trapped at the cell body due to the lack of recycling back to the axon terminals by kinesin, since kinesin transport is necessary to deliver dynein to the plus ends of microtubules. The decrease in KIF1A and KIF5B levels at the cell bodies of RGCs may thus amplify the anterograde transport deficits [56]. Notably, the progressive degeneration of cone and rod photoreceptors lacking KIF3A [59] highlights the importance of the adequate function of kinesin in the visual pathway. In a model of retinal neurotoxicity induced by N-methyl-D-aspartate, there is an upregulation of KIF5B levels in the retina, and a downregulation in the optic nerve, indicating that a depletion of KIF5B may precede axonal degeneration in the optic nerve [60]. Therefore, it is expected that any imbalance in the kinesin content due to diabetes may have an impact in axonal transport in the retina.

In the hippocampus of STZ-induced diabetic rats, KIF1A and KIF5B expression and immunoreactivity increase, whereas dynein is not altered [55]. This increase in kinesin levels may be due to the imbalance in protein degradation/synthesis, or may alternatively function as a compensatory mechanism as an attempt of the system to reestablish the basal protein levels [55]. In primary hippocampal neuronal cultures exposed to hyperglycemic conditions, an increase in the number of fluorescent KIF1A and synaptotagmin-1 accumulations in the axons was described, in parallel with a decrease in KIF5B, synaptophysin, and SNAP-25 immunoreactivity [55]. The accumulation of KIF1A may be due to impairments in motor function and/or to changes in microtubule network [55]. However, the interpretation of in vitro studies mimicking hyperglycemia must be cautious, once neurons must be cultured already in unnaturally high glucose concentrations in order to survive in culture.

The alterations in kinesin motor proteins in the retina and hippocampus indicate that the anterograde axonal transport may be compromised and could help to explain the decrease in the levels of synaptic proteins in nerve terminals induced by diabetes [55, 61, 62]. Consequently, a decrease in the number of synaptic vesicles transported anterogradely may account for changes in synaptic transmission and contribute for synaptic dysfunction in diabetes.

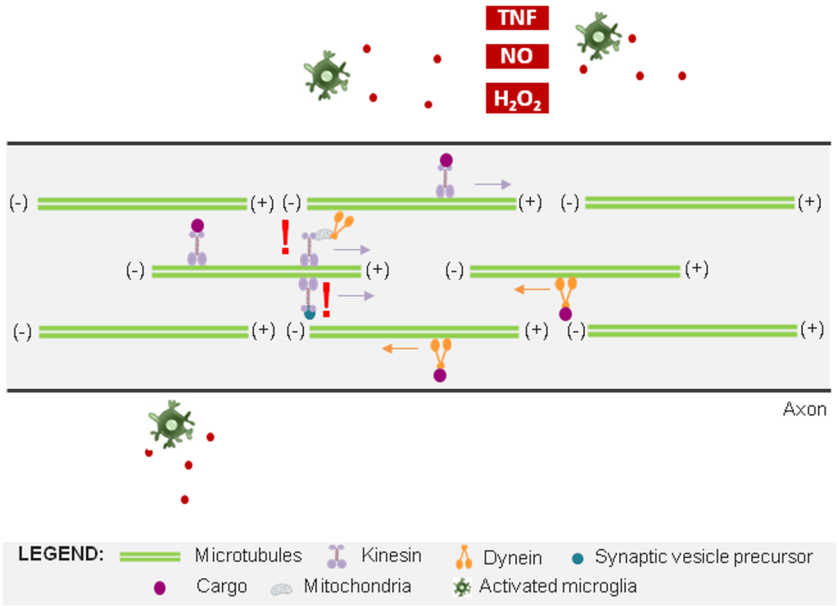

Fig. 3 Microglia-driven inflammation and axonal transport impairment. In hippocampal cultures, the release of pro-inflammatory mediators by microglia, such as nitric oxide (NO), tumor necrosis factor (TNF), and hydrogen peroxide (H_2O_2), impairs the axonal transport of synaptic vesicles precursors and mitochondria. Considering the increased release of pro-inflammatory molecules in diabetes, similar mechanisms may occur in this pathology, contributing to the impairment in axonal transport

The impact of diabetes in mitochondrial axonal transport in the CNS remains to be elucidated. Regarding this issue, in conditions mimicking hyperglycemia, no alterations were observed in the number of mitochondria or in their distribution in hippocampal axons [55]. In diabetes, neuroinflammation may also play a role inducing mitochondrial transport

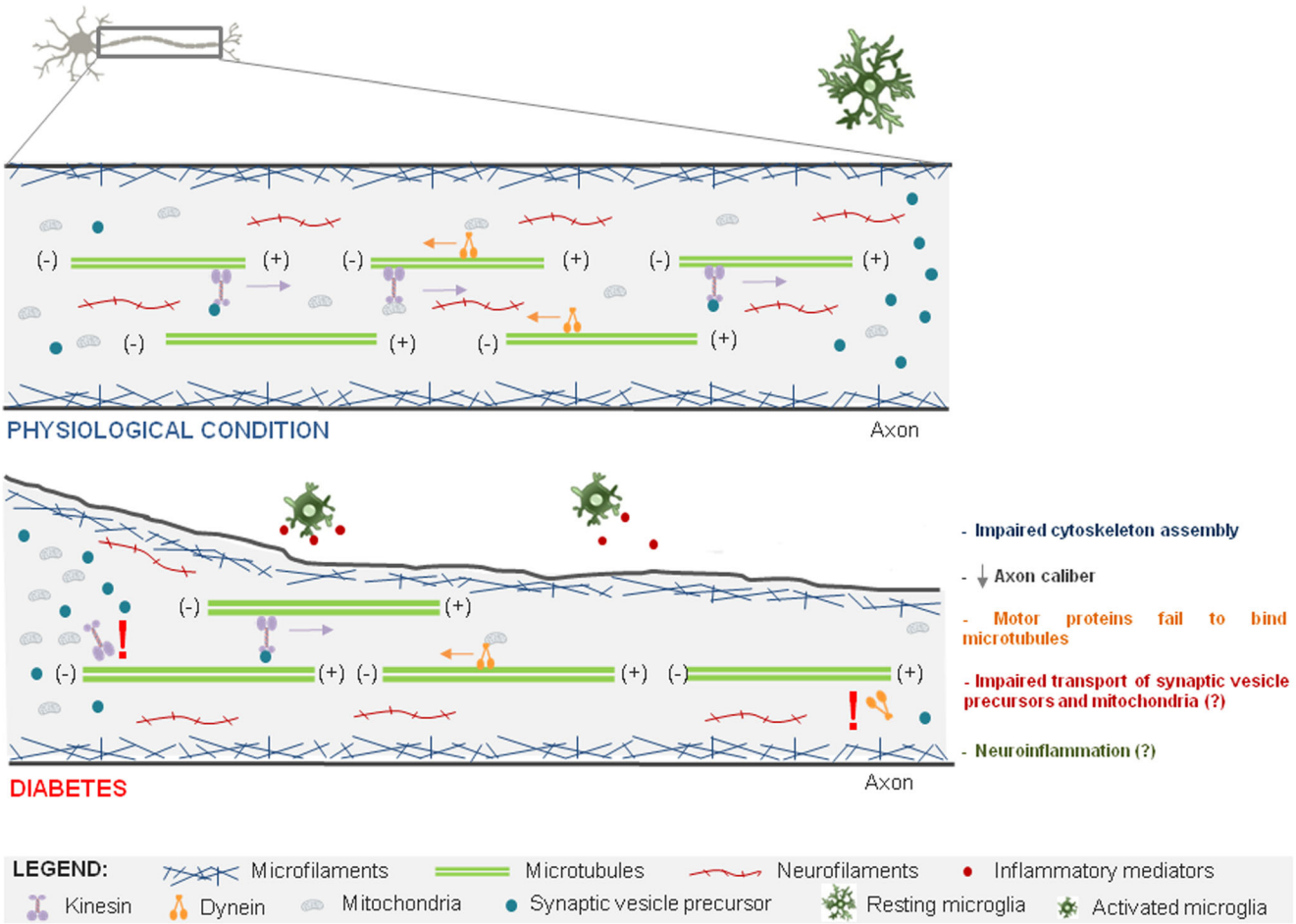

Fig. 4 Putative mechanisms underlying axonal transport impairments in diabetes. Several alterations can contribute to the disruption of axonal transport, including alterations in the cytoskeleton, molecular motor proteins, mitochondrial transport, and possibly, microglia-driven neuroinflammation

alterations in neurons. Tumor necrosis factor (TNF), a pro-inflammatory cytokine, was already reported to induce mitochondrial clustering around the nucleus in murine fibrosarcoma cell line L929, by impairing kinesin-mediated transport [63]. It is crucial to further investigate the impairment in mitochondrial transport in diabetes, once it will likely lead to a decrease in the number of mitochondria located in the axon, reducing the ATP supply to motor proteins, which will impair not only the transport of mitochondria but also other cargoes.

Concerning the contribution of neuroinflammation to diabetes-induced impairments in axonal transport, there is an evident lack of studies. However, it is accepted that diabetes triggers an inflammatory response, namely, in the brain and retina, by the detection of increased levels of pro-inflammatory cytokines, such as interleukin-1β and TNF in the hippocampus and retina of diabetic rats [64, 65]. TNF was already described to impair kinesin activity by hyperphosphorylation of kinesin light chain, suggesting that the axonal transport mediated by kinesin motor proteins may be regulated by the activation of TNF receptor-1 signaling pathways [66]. Additionally, the exposure of hippocampal neurons to TNF inhibits mitochondrial and synaptophysin axonal transport by dissociating KIF5B from microtubules, in a manner dependent on the phosphorylation of c-Jun N-terminal kinase [66]. The transport of mitochondria is also affected by hydrogen peroxide in hippocampal cultures [67].

Besides these pro-inflammatory mediators, it was further described that nitric oxide derived from microglia, the resident immune cells of the CNS, impairs axonal transport of synaptic vesicle precursors in hippocampal neurons [68] (Fig. 3). Since diabetes induces microglial activation, both in the brain and in the retina [69, 70], the disturbance of axonal transport by microglia-derived inflammatory mediators may therefore contribute for synaptic dysfunction in the context of diabetes.

In summary, in the CNS, the alterations in axonal transport in diabetes may contribute to neuronal dysfunction, namely, by altering the transport of cytoskeletal components. The visual pathways are particularly affected by diabetes, with an impairment in both retrograde and anterograde transport between the retina and brain.

Conclusions

Impairments in the axonal transport are early events in diabetes that may contribute for the development and progression of the associated complications, such as diabetic neuropathy, retinopathy, and encephalopathy. Several alterations can contribute to the disruption of axonal transport, including alterations in the cytoskeleton, molecular motor proteins, mitochondrial transport, and, possibly, neuroinflammation (Fig. 4). However, little is known about the cellular and molecular mechanisms associated with axonal transport impairments in diabetes. Thus, it is important to invest in this field, applying novel techniques such as high-resolution live-imaging and manganese-enhanced magnetic resonance imaging [27, 28], once understanding the mechanisms responsible for axonal transport impairments in diabetes may be crucial to develop novel neuroprotective strategies.

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