Glial Cells

Glial cells are an important source of growth factors, particularly during development when the growing axons have not yet reached their targets.

From: Basic Neurochemistry (Eighth Edition), 2012

Related terms:

Oligodendrocyte, Microglia, Astrocyte, Glutamic Acid, Eicosanoid Receptor-, Schwann Cell, Enzymes, Central Nervous System, Axon, Protein

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Glial Cells

R.D. Fields, in Encyclopedia of Human Behavior (Second Edition), 2012

Schwann Cells

Schwann cells are the glial cells that form the myelin sheath on axons outside the brain. Unlike oligodendrocytes, Schwann cells do not have multiple cellular extensions, but instead each cell engulfs a segment of axon and forms a multilayered myelin sheath around it (**Figure 3**). Small diameter axons, which conduct impulses slowly, do not have a myelin sheath, yet they are not bare. Other Schwann cells, which do not form myelin, engulf multiple small diameter axons into bundles. Another type of specialized nonmyelin forming Schwann cell encases the synaptic endings on muscles, much like astrocytes surrounding synapses in the brain. Schwann cells perform most of the functions of astrocytes, oligodendrocytes, and microglia in the brain, as none of these glia exists outside the CNS. Schwann cells are not found in the CNS, so they will not be discussed in the context of this article, which is concerned with glia in human behavior. These cells are named after Theodore Schwann (1810–1882), who also expounded the theory that all organisms are composed of cells.

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Nervous System

Catherine A. Picut, ... Amera K. Remick, in Atlas of Histology of the Juvenile Rat, 2016

Glial Cells

Glial cell development is restricted to the postnatal timeframe, and occurs in a surge from PND 7 through 21 (Bandeira et al., 2009; Haddara, 1956; Schade et al., 1964) when 90% of all nonneuronal cells are added to the brain. Glial cells include astrocytes, oligodendrocytes, and microglia. Like neurons, certain glial cells arise from the stem cells of the germinal matrix. Once generated, the glial cells migrate into position, and become postmitotic as they acquire mature phenotype and physiologic function (Molofsky and Deneen, 2015). Unlike neurons, some glial cells such as astrocytes can divide or proliferate *after* they migrate (Molofsky and Deneen, 2015). Therefore, mitotic activity in the brain generally involves the glial cells and not neurons.

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Mechanisms of Glial Death and Protection

C. Matute, in Primer on Cerebrovascular Diseases (Second Edition), 2017

Abstract

Glial cells outnumber neurons in the mammalian central nervous system and are key to maintaining tissue homeostasis. They also support neurotransmission, adult neurogenesis, and immune surveillance, among a pleiad of functions. Glial cells contribute to the pathophysiology of cerebrovascular diseases by driving neuroinflammatory responses and contributing to tissue repair. In turn, glial cells themselves undergo primary and secondary cell death as a consequence of impaired blood supply, and thus contribute substantially to overall nervous tissue damage. The aim of this chapter is to describe major cellular and molecular mechanisms of glial cell death and protection, particularly as they relate to stroke.

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Water Homeostasis Dysfunction in Epilepsy

Devin K. Binder, in Brain Edema, 2017

Abstract

Glial cells are involved in many important physiologic functions, such as sequestration and/or redistribution of K_+ during neural activity, neurotransmitter cycling, and provision of energy substrates to neurons. Several recent lines of evidence strongly suggest that changes in glial cells potentially contribute to epilepsy. First, many studies now link glial cells to modulation of synaptic transmission. Second, functional alterations of specific glial membrane channels and receptors have been discovered in epileptic tissue. Third, direct stimulation of astrocytes has been shown to be sufficient for neuronal synchronization in epilepsy models (although see Fiacco et al., 2007). Thus, if the cellular and molecular mechanisms by which glial cells (especially astrocytes) modulate excitability are better understood, specific antiepileptic therapies based on modulation of glial receptors and channels can be contemplated. It is likely that therapies directed to glial cells would have fewer deleterious side effects than current therapies targeting neurons.

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Hypoparathyroidism

Fadil M. Hannan, Rajesh V. Thakker, in Genetics of Bone Biology and Skeletal Disease (Second Edition), 2018

5.2.1 Mouse Model With Gcm2 Deletion

Gcm2–/– mice lack parathyroid glands and develop hypocalcemia and hyperphosphatemia as observed in hypoparathyroidism.[125,126] However, despite their lack of parathyroid glands, *Gcm2*–/– mice do not have undetectable serum PTH levels.[125,126] This endogenous level of PTH in the *Gcm2*–/– mice is too low to correct the hypocalcemia, but exogenous continuous PTH infusion could correct the hypocalcemia.[125] Interestingly, there were no compensatory increases in PTHrP or $1,25(OH)_2D_3$. These findings indicate that *Gcm2*–/– mice have a normal response (and not resistance) to PTH. Long-term treatment of the *Gcm2*–/– mice with $1,25(OH)_2D_3$ restored the serum calcium concentrations to normal and reduced the serum PTH levels, thereby indicating that the production of PTH can be downregulated.[125] This Gcm2-in-

dependent auxiliary source of PTH production has been shown to be from the medullary thymic epithelial cells, in which PTH is expressed as a self-antigen for negative selection.[126]

The specific role of *Gcm2* in the development of the parathyroids from the 3rd pharyngeal pouch has been further investigated by studying the expression of the Hoxa3-Pax1/9-Eya1 transcription factor and sonic hedgehog–bone morphogenetic protein 4 (Shh–Bmp4) signaling networks.[43] These studies have revealed that *Gcm2* expression begins at E9.5 in the dorsal anterior pharyngeal endoderm of the 3rd pouch and is maintained in the presumptive mouse parathyroid domain at later stages,[127] and that at E12.0 *Gcm2*–/– embryos have a parathyroid-specific domain, but that this parathyroid domain undergoes coordinated programmed cell death (apoptosis) by E12.5 in the *Gcm2*–/– mouse embryos.[43] Moreover, the expression of the transcription factors Hoxa3, Pax1, Pax9, Eya1, and Tbx1, and of Shh and Bmp4 was normal in the 3rd pharyngeal pouches of these *Gcm2*–/– mouse embryos. These findings indicate that the Hoxa3-Pax1/9-Eya transcription factor cascade, the transcription factor Tbx1 and the Shh-Bmp4 signaling network, all act upstream of Gcm2.[43] Indeed it has been shown that *Hoxa3* is required for the initiation of *Gcm2* expression in the 3rd pouch endoderm, and both *Hoxa3* and *Pax1* are required for the maintenance of *Gcm2* expression.[128] Moreover, these studies have revealed that Gcm2 has a role in promoting differentiation and survival of parathyroid cells in the developing embryo.[43] Thus, *Gcm2* is required for the differentiation of parathyroid precursor cells in the parathyroid specific domain, but is not required for initial patterning or expression of differentiation markers, such as the CaSR in the common parathyroid/thymus primordia.[43] The target genes of mammalian GCMB/Gcm2 are largely unknown. However, studies that utilized cultured primary parathyroid cells from hyperplastic glands of patients with chronic kidney disease[129] have demonstrated that downregulation of GCMB expression achieved by infection with lentivirus expressing shRNA for GCMB, resulted in downregulation of CaSR expression, thereby suggesting that one of the functions of GCMB may be to maintain high levels of CaSR expression in parathyroid cells.[129] These findings are supported by studies in cotransfected HEK-293, in which exogenous GCMB was able to transactivate reporter constructs that contained CaSR promoter DNA sequences, which encompassed GCMB response elements.[130]

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Retinal Glia

E.A. Newman, in Encyclopedia of Neuroscience, 2009

Introduction

Glial cells outnumber neurons in the central nervous system (CNS) by □10 to 1. Traditionally, glia were believed to provide only passive structural and metabolic support for neurons. Recent work has demonstrated, however, that glial cells in the retina as well as in the brain interact actively with neurons and have many essential functions.

There are three principal types of glial cells in the mammalian retina: Müller cells, astrocytes, and microglial cells. Müller cells are the most prominent retinal glial cell. They are a specialized form of radial glia which span nearly the entire depth of the retina. Astrocytes, the second type of retinal macroglial cell, are present only in species having a retinal circulation and, in these species, are restricted largely to the nerve fiber layer at the inner boundary of the retina. Microglia, the third type of retinal glial cell, are present in the nerve fiber layer and the inner and outer plexiform layers of the retina. Oligodendrocytes, the glial cells that form the insulating sheath of myelinated axons in the CNS, are completely absent from the retina, except in those species, including rabbit and guinea pig, possessing myelinated axons in the nerve fiber layer.

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Tissues

Bruce M. Carlson MD, PhD, in The Human Body, 2019

Glial Cells

Glial cells have long remained the most enigmatic component of the nervous system (Fig. 2.29). By default, they have been defined as any kind of nervous tissue cell that is not a neuron. Their total numbers at least equal the number of neurons within the CNS,[3] but the proportions depend upon the part of the brain. For example, in the cerebral cortex, glial cells outnumber neurons by almost 3:1, whereas in the cerebellum the ratio is reversed.

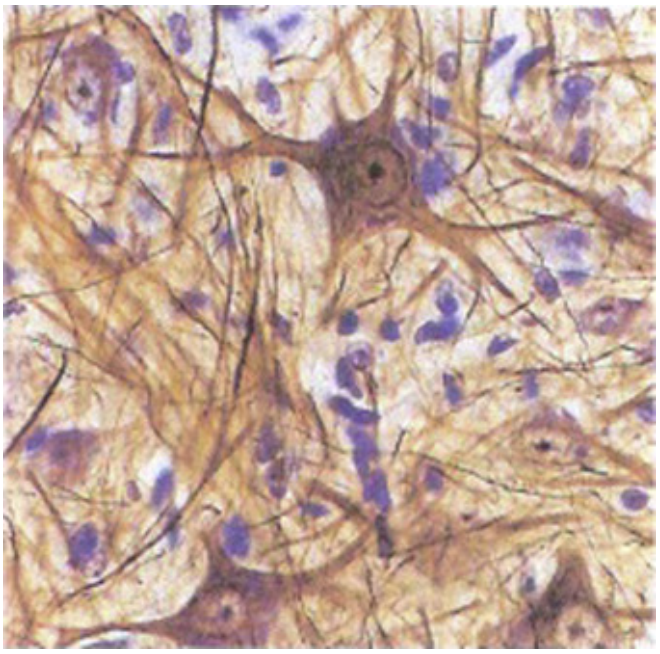

Figure 2.29. Photomicrograph of neurons (large brown structures) and glial cells (smaller blue structures).From Waugh and Grant (2014), with permission.

Commonly, six types of glial cells have been defined. Four types of them are located in the brain and spinal cord, and two are found in the PNS (Table 2.5). Astrocytes and oligodendrocytes are closely associated with neurons and arise in the embryo from the same precursor cells as do neurons. Tiny **microglial cells** are derived from a different embryonic stem cell lineage and serve as scavengers of dead cellular material within the brain. The fourth glial cell type, **ependymal cells**, is arranged like an epithelium and lines the central canal of the brain and spinal cord. Ependymal cells produce cerebrospinal fluid, but in recent years the ependymal epithelium has also been found to be associated with neuronal stem cells. Within the cerebral cortex, 76% of the glial cells consist of oligodendrocytes, 17% astrocytes, and 7% microglia. The glial cells of the PNS are called Schwann cells and **satellite cells**. Schwann cells play the same functional role in the PNS as oligodendrocytes do in the CNS, namely providing an insulating cover of myelin over axons and dendrites. Satellite cells surround the cell bodies of peripheral neurons; their function remains obscure.

Table 2.5. Types of Glial Cells

Cell Type	Function
Within Central Nervous System	
Oligodendrocyte	Myelination within CNS
Astrocyte	Creation of blood–brain barrier
Mechanical support of neurons	
Stimulate synapse formation	
Modulate neuronal signaling	
Metabolize nutrients for neurons	
Secrete growth factors	
Form scars after damage to CNS	

Microglia	Remove debris from damaged or dead cells
Produce signaling molecules (cytokines)	
Ependymal cells	Secrete and absorb cerebrospinal fluid
Stem cell function	
Within Peripheral Nervous System	
Schwann cells	Myelination within PNS
Production of growth factors	
Satellite cells	Surround, nourish, and support peripheral neurons

Astrocytes, which have many processes occurring off the cell body, come in two main shapes. In gray matter, the processes of what is called protoplasmic astrocytes are relatively fleshy, and they contact both synapses and blood vessels. The astrocytes of white matter have much thinner processes, which contact both blood vessels and nodes of Ranvier. Many functions are attributed to astrocytes. A major one is creating the blood–brain barrier, which prevents many cells and large molecules from reaching the nervous tissues from the blood (Fig. 2.30). Astrocyte processes around synapses promote their initial development and modulate their ongoing function by controlling levels of K_+ and some neurotransmitters. After injury to the brain or spinal cord, astrocytes form scar-like masses that inhibit the regeneration of severed axons and dendrites.

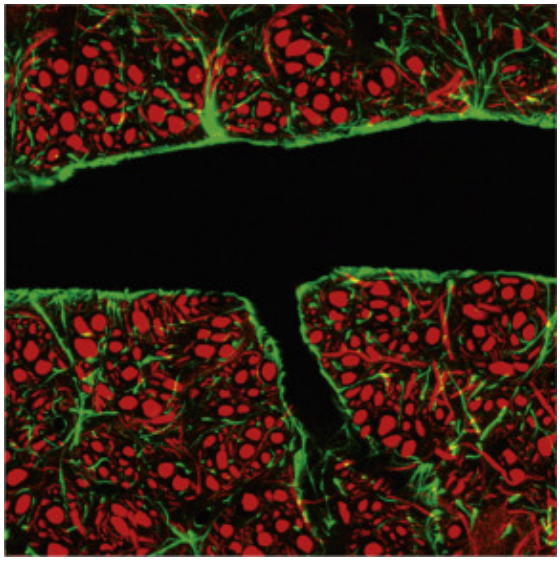

Figure 2.30. Fluorescence micrograph, showing the blood–brain barrier. Red, neurons; green, astrocytes, which form a tight barrier between the blood (black space) and the brain tissue.From Underwood (2015), with permission.

In order to function properly, within both the CNS and PNS, nerve processes are surrounded by a lipid-rich cellular insulation, called **myelin**. The Schwann cells in the PNS and the oligodendrocytes in the CNS wrap around the axons and dendrites in a manner that in cross-section very much resembles layers of electrical tape wound around a wire (Fig. 2.31). Spaces between these cells (**nodes of Ranvier**) and also the

insulation that the Schwann cells provide constitute an important structural basis for the transmission of an electrical signal (action potential) down a nerve process.

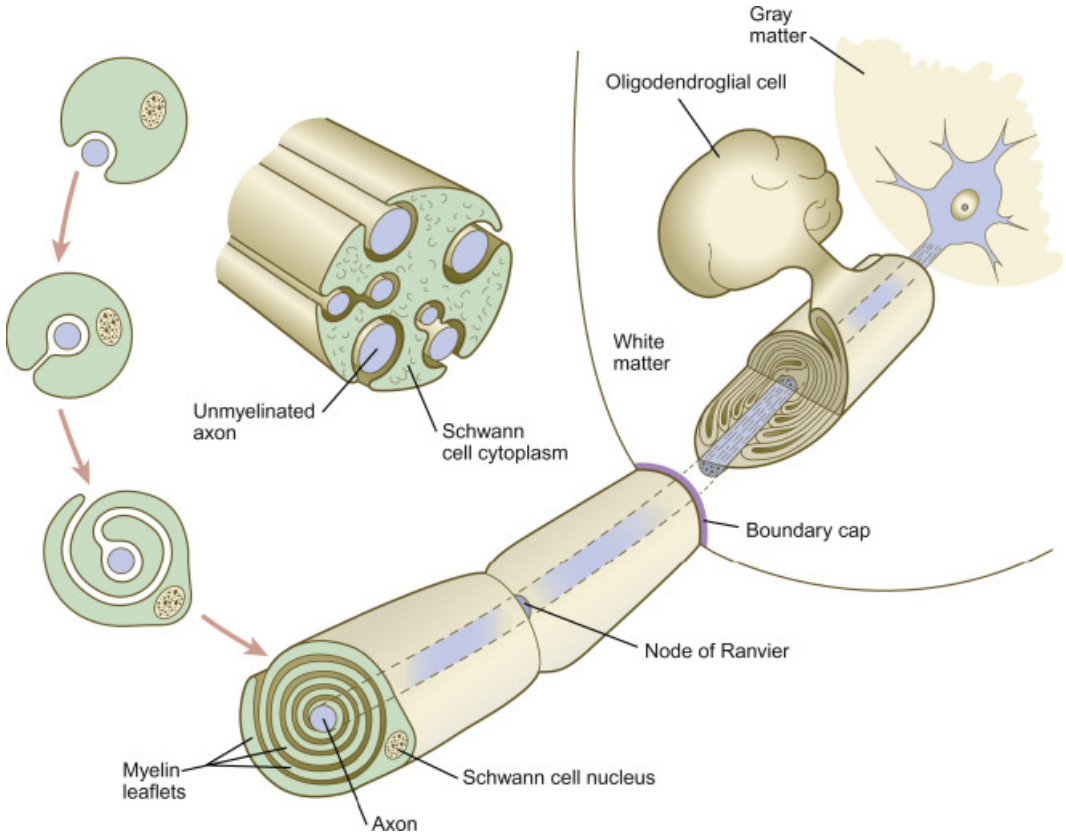

Figure 2.31. Myelination the peripheral nervous system by wrappings of Schwann cells and in the central nervous system by similar wrappings of oligodendroglial cells.From Carlson (2014), with permission.

In peripheral nerves, the cell bodies of the Schwann cells lie outside the multiple layers of myelin sheathing. These are collectively covered by a basal lamina of their own making and a thin layer of collagen fibers. This layer is called the **endoneurium** (Fig. 2.32), and constitutes the first layer of the fasciae that provide mechanical strength to the actual nerve. Surrounding bundles of axons, each covered with its own endoneurium, is a thicker and tougher layer of connective tissue, called the **perineurium**. Finally, ensheathing many bundles of nerve fibers is a still thicker **epineurium**, which surrounds the entire nerve. These coverings are of great importance to nerve surgeons, who suture the severed ends of perineurium or epineurium together to provide appropriate channels for regenerating nerve fibers after trauma to a nerve.

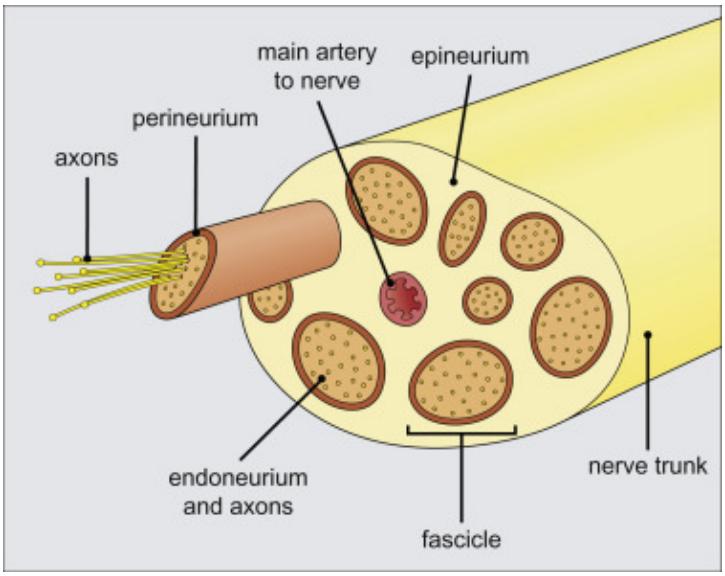

Figure 2.32. Diagram showing the relationships among the connective tissue sheaths within the cross-section of a peripheral nerve fiber.From Stevens and Lowe (2005), with permission.

Figure 2.33. Functions of the sodium-potassium pump in a nerve cell. As Na_+ leaves and K_+ enters the cell, ATP is converted to ADP, with the release of energy.From Guyton and Hall (2016), with permission.

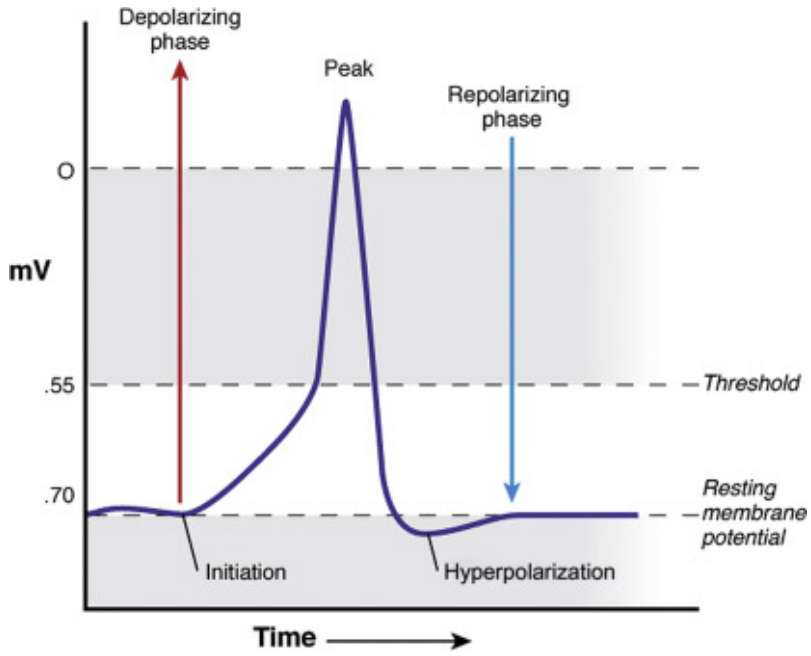

Figure 2.34. Diagram of an action potential along the axon of a nerve.Redrawn from Purves et al. (2008), with permission.

Figure 2.35. Conduction of an action potential down an unmyelinated axon. It begins with depolarization of the axonal membrane at point A at the top ($t = 1$). Passive current flow depolarizes the membrane until the opening of new Na_+ channels at point B generates an action potential at that site ($t = 2$). This process is repeated ($t = 3$), as the action potential is propagated at point C.From Purves et al. (2008), with permission.

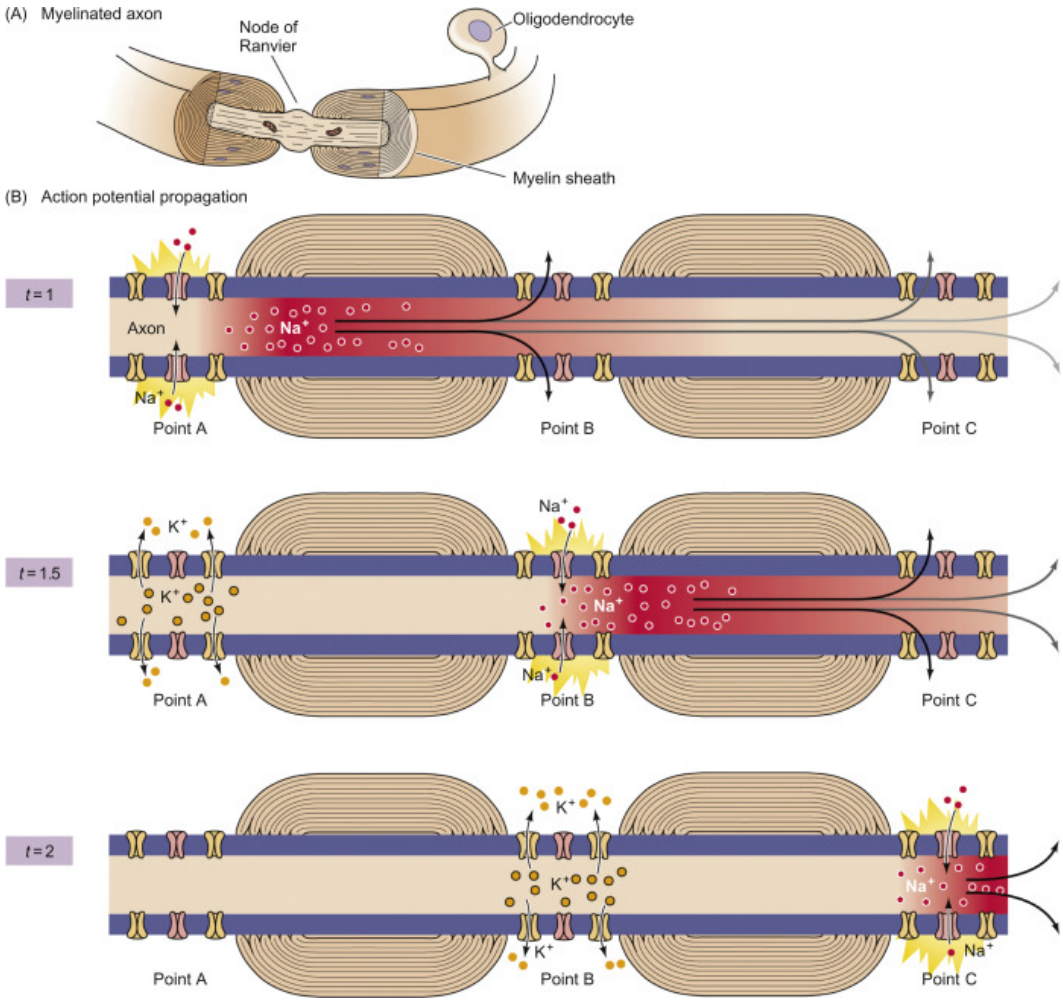

Figure 2.36. Propagation of an action potential down a myelinated axon by means of saltatory conduction. The myelin covering prevents the leakage of current through the axonal membrane, but at the nodes of Ranvier (see Part A), the lack of myelin allows the activation of sodium channels and the propagation of the action potential from one node to the next one down the axon. This mode of propagation of the action potential greatly speeds up the overall rate of transmission.From Purves et al. (2008), with permission.

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Development

D.E. Featherstone, K.S. Broadie, in Comprehensive Molecular Insect Science, 2005

2.3.3.2 Peripheral Glia and Motor Neuron Pathfinding

Peripheral glia arise from the neural crest in vertebrates and the lateral edge of the CNS in insects. Peripheral glia in Drosophila are molecularly distinct from CNS glia. Both express unique proteins, such as gliotactin in the peripheral glia (Auld *et al.*, 1995), and wrapper in the central glia (Noordermeer *et al.*, 1998). In *Drosophila*, each hemisegment neuromere has two peripheral nerve roots, by which motor axons exit and sensory axons enter the CNS. Several classes of glial cells are associated with these peripheral nerves at different points. First, there are a small number of glial cells associated with the segmental (middle of neuromere) and intersegmental (neuromere boundary) nerve roots, where they diverge from the main CNS axonal tracts. These cells are present prior to axon extension, and ablation of this glial class in the grasshopper prevents formation of the peripheral nerve (Bastiani *et al.*, 1986). Second, the so-called "exit glia" are located just outside the CNS, where the segmental and intersegmental neurons diverge into peripheral axonal pathways. In addition, there are several glial cells that associate with peripheral axonal pathways, and enwrap the axons once the paths have been established.

Most peripheral glia are born in the CNS near the lateral exit points for the peripheral nerves. Lineage analyses in *Drosophila* have shown that approximately 8–10 (some variation) peripheral glia per hemisegment arise specifically from neuroblasts 1–3 and 2–5 (Schmid *et al.*, 1999; Sepp *et al.*, 2001). At least one further glial cell is born in the periphery, associated with the ISN, and remains in its birth place through later development (Hidalgo, 2003). During mid-embryogenesis, the centrally born glia migrate over great distances to their final peripheral locations. These cells migrate as a continuous chain of glia, with the pioneering glial cells actively exploring the environment using Actin-based filopodia (Sepp and Auld, 2003). The small GTPases RhoA and Rac1 mediate the Actin cytoskeletal rearrangements required for this migration (Sepp and Auld, 2003).

In the CNS, the immature glia seem to act as intermediate guidepost cells for pioneer motor axons migrating into the periphery. Peripheral glia prefigure axon paths through the CNS/periphery transition zone through which axons migrate into and out of the CNS. When peripheral glia are ablated early, via targeted expression of the cell death genes *grim* and *ced-3*, motor axon trajectories are initially perturbed, although later largely corrected (Sepp *et al.*, 2001). This suggests that peripheral glia do act as early guideposts for motor axons, but that other cues in the periphery are sufficient to guide these axons to their correct target muscles. Sensory axons entering the CNS are also disrupted, but these pathfinding errors are not corrected (Sepp *et al.*, 2001). Following this early guidance, motor axon growth cones extend past the immature glia and begin to pathfind into the developing muscle field. At this point, these motor axons appear to now serve as the guidance substrate for

the migration of glial cells into the periphery (Sepp *et al.*, 2000). For example, in *Drosophila*, the aCC neuron pioneers the ISN during stage 12 (□40% development). Once it has passed the 8–10 glia at the CNS exit point, the glia begin to follow the aCC axon into the periphery (Sepp *et al.*, 2000). Importantly, the glial growth cones never appear to extend past the aCC pioneer growth cone, suggesting that the aCC is acting as the substrate for glial cell migration. During stages 13–15 (47–60% development), the peripheral glia first follow the outgrowing motor axons through the ventral field, and then the mixed motor/sensory axons, through the dorsal field (Sepp *et al.*, 2000).

In *Drosophila*, genetic mutations that impair glial differentiation result in profound defects in peripheral nerves. For example, mutations in the homeobox transcription factor *gcm* gene disrupt the specification of most glia and cause severe axonal defasciculation and pathfinding errors (Jones *et al.*, 1995). However, these mutations affect all glial cells, not just the peripheral glia selectively, so the cause of these defects is uncertain. Ablation or genetic disruption of peripheral glia results in defasciculated axon tracts (Sepp *et al.*, 2001), but it has yet to be genetically proven that peripheral glia mediate axonal pathfinding. Indeed, the developmental profile given above suggests the opposite: in peripheral axons, first motor axons ventrally and then sensory axons dorsally provide guidance for the peripheral glia to reach their mature destinations.

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Neuroglia

Jean-Pierre Barral, Alain Croibier, in Manual Therapy for the Cranial Nerves, 2009

The learning process

Glial cells play a determining role in the intelligence of the human species, which possesses the largest proportion of glial cells in the animal kingdom.

From the neuronal point of view, Albert Einstein's brain, autopsied in the 1980s, was found to be no different from those of the layman. The number and appearance of his neurons were nothing out of the ordinary. Only those areas of the brain dedicated to the most complex tasks were shown to have an incredibly high proportion of glial cells.

The cortex tends to increase in volume in cerebral zones that have undergone an intense learning process. In these same areas, neuron density tends to diminish. It appears that the glial cells form special contact zones for the neurons. The more

complex the task, the more astrocytes appear to intervene in the communication between neurons. In other words, faced with a new or complex situation, the astrocytes also adapt.

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Calcium Homeostasis in Glia

A.C. Charles, K.C. Brennan, in Encyclopedia of Neuroscience, 2009

Sources of Calcium in Glial Cells

Glial-cell Ca^{2+} signals may be generated by release of Ca^{2+} from intracellular stores, influx of Ca^{2+}, or a combination of the two. An individual Ca^{2+} response involves a complex interplay between different sources and sinks for Ca^{2+}. Because glial cells are 'nonexcitable cells' – that is, most glial cells don't generate action potentials – their Ca^{2+} signaling typically relies on release of Ca^{2+} from intracellular stores to a greater extent than in neurons, where Ca^{2+} signaling depends more on Ca^{2+} influx that is related to changes in membrane potential. A typical glial Ca^{2+} response is therefore slower and more sustained than that of a neuron.

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