REVIEW ARTICLE

Neurotransmitter Signaling in White Matter

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White matter (WM) tracts are bundles of myelinated axons that provide for rapid communication throughout the CNS and integration in grey matter (GM). The main cells in myelinated tracts are oligodendrocytes and astrocytes, with small populations of microglia and oligodendrocyte precursor cells. The prominence of neurotransmitter signaling in WM, which largely exclude neuronal cell bodies, indicates it must have physiological functions other than neuron-to-neuron communication. A surprising aspect is the diversity of neurotransmitter signaling in WM, with evidence for glutamatergic, purinergic (ATP and adenosine), GABAergic, glycinergic, adrenergic, cholinergic, dopaminergic and serotonergic signaling, acting via a wide range of ionotropic and metabotropic receptors. Both axons and glia are potential sources of neurotransmitters and may express the respective receptors. The physiological functions of neurotransmitter signaling in WM are subject to debate, but glutamate and ATP-mediated signaling have been shown to evoke Ca^{2+} signals in glia and modulate axonal conduction. Experimental findings support a model of neurotransmitters being released from axons during action potential propagation acting on glial receptors to regulate the homeostatic functions of astrocytes and myelination by oligodendrocytes. Astrocytes also release neurotransmitters, which act on axonal receptors to strengthen action potential propagation, maintaining signaling along potentially long axon tracts. The co-existence of multiple neurotransmitters in WM tracts suggests they may have diverse functions that are important for information processing. Furthermore, the neurotransmitter signaling phenomena described in WM most likely apply to myelinated axons of the cerebral cortex and GM areas, where they are doubtless important for higher cognitive function.

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Introduction

White matter (WM) is defined as a tract of myelinated axons—WM appears opaque or dense due to the fatty myelin in anatomical sections and in brain scans. Notwithstanding this, myelination is not restricted to WM and is also critical to rapid communication and integration in grey matter (GM) areas, such as in axons in the cortical GM and hippocampus. Hence, many aspects of neurotransmitter signaling to be covered in this review have resonance in GM and higher cognitive function. Indeed, in the human brain WM is a prominent feature of the cerebral cortex, the seat of higher intelligence. Myelination of GM is also evident in rodents, but discrete WM tracts are not pronounced in the cerebral cortex. As a general concept, WM are simply concentrations of myelinated axons bundled together into tracts that interconnect areas of GM. The molecular physiology of myelinated axons will be very similar in WM and GM, and they will be subject to the same neurotransmitter signaling phenomena that is the subject of this review. The main cells associated with myelinated axons are the myelinating oligodendrocytes and oligodendrocyte precursor cells (OPCs), or NG2-glia (~10–20% of oligodendrocyte lineage cells are estimated to be OPCs), together with astrocytes and small populations of microglia. In tracts such as the optic nerve, most if not all axons are myelinated, whereas other tracts can contain both myelinated and small diameter unmyelinated axons. Astrocytes appear first in development, followed by OPCs that differentiate into myelinating oligodendrocytes mainly during the postnatal period, although they continue to generate oligodendrocytes slowly throughout adult life; in rodents, myelination in the forebrain continues until at least 6 to 12 months, and in the human cortex up until 50 years of age, after which myelination declines. A major disease of WM is Multiple sclerosis (MS), a demyelinating disease that results in a devastating loss of function (Lassmann, 2014). However, the incidence of stroke is far greater and the

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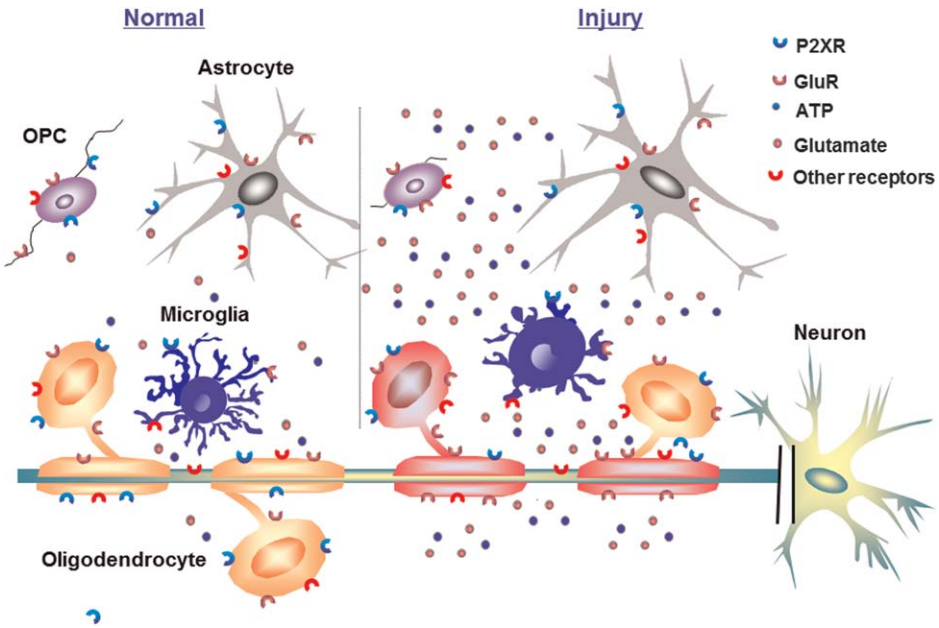

FIGURE 1: Neurotransmitter signaling in white matter pathophysiology. White matter axons, macroglia, microglia, and myelin express a large repertoire of neurotransmitter receptors whose functional significance remains elusive. Among them, ionotropic glutamate receptors and P2X7 receptors have been partially characterized and their localization is relatively well known. Their activation leads to an overall increase in cytosolic Ca^{2+} which in pathological conditions can lead to primary or secondary glial cell death and axonal damage; in particular, oligodendrocytes and their progenitors (OPC) are highly vulnerable to Ca^{2+} overload. Under normal conditions (left), glutamate is taken up by glutamate transporters and ATP readily degraded by ectoATPases which prevent overactivation of glutamate and P2X7 receptors, respectively. In white matter injury (right), increased extracellular levels of glutamate and/or ATP, and other transmitters, leads to overactivation of their receptors which can lead to injury (depicted in pink for oligodendrocytes and myelin). See text for further details. Abbreviations: GluR, glutamate receptor; OPC, oligodendrocyte progenitor cell.

majority of strokes affect myelinated axons, which are also the seat of developmental lesions associated with cerebral palsy (Back and Rosenberg, 2014). In addition, myelin loss or disruption are also primary pathological features of leukodystrophies, as well as traumatic brain injury and spinal cord injury (Kou and VandeVord, 2014), and is associated with dementias (including Alzheimer's disease) and neuropsychological diseases, such as bipolar disorder and schizophrenia (Haroutunian et al., 2014).

One of the most commonly studied WM preparations is the optic nerve, which connects the eye to the brain, and to lesser extents the corpus callosum, which forms a large commissure connecting the two hemispheres of the cerebrum, and the dorsal column of the spinal cord. Notably, the optic nerve does not contain neuronal cell bodies or synapses, although this is not the case for all WM structures (von Engelhardt et al., 2011). It is surprising that neurotransmitter-mediated signaling is prominent in the optic nerve and other WM areas studied, since neurotransmitter signaling is generally considered to be an exclusive function of neurons confined to synapses. Most evidence points to major roles for glutamate and ATP, but numerous other neurotransmitters are also implicated in WM signaling, including GABA and norepinephrine (Fig. 1). There is a clear role for glutamate and ATP in WM pathology, for example in ischemia and demyelination. In contrast, the primary physiological functions of neurotransmitters in WM remain elusive. In this review, we will focus on the potential physiological functions of glutamate- and ATP-mediated signaling and provide an overview of other key neurotransmitters.

Multiple Neurotransmitters are Present in WM

Reports on the effects of neurotransmitters on WM are plentiful, in particular during development. As described below, isolated WM preparations show functional responses to a variety of neurotransmitters, although localization of receptor expression can be difficult. *In vitro* studies largely produced in the 1980s reported numerous cases of astrocytes and/or oligodendroglia that either responded to neurotransmitter agonists or expressed receptor protein/mRNA (Domingues et al., 2010; Hertz et al., 1984; Salm and McCarthy, 1989; Williamson et al., 1998). However, caution must be used in extrapolating what glial cells are capable of doing in culture conditions from what they actually do in the CNS, and we have compiled a list of glutamatergic/purinergic (Table 1) and non-glutamatergic/purinergic WM receptor expression studies (Tables 2 and 3), restricted to reports that have confirmed

TABLE 1: Glutamate Receptors and Purinoceptors in White Matter in Health and Disease

	Cell type, model, or preparation	Receptor/taget	Evidence/MECHANISM	References
Health	Myelinated spinal cord axons	AMPA/Kainate	Regulation of intraaxonal calcium	Ouardouz et al., 2009a,b
	Axons	AMPA/Kainate	Broadening action potentials	Sasaki et al., 2011
	OPCs	Glutamate and ATP receptors	Initiate myelination	Wake et al., 2011
	Myelin	NMDA	Reduced calcium permeability	Káradottir et al., 2005; Salter and Fern, 2005; Micu et al., 2006
	OPCs, oligodendrocytes	mGluR	Expression lower in mature cells	Deng et al., 2004
	Astrocytes and oligodendrocytes in situ	P2Y1	Immunocytochemistry	Morán and Matute, 2000
	Oligodendrocytes and myelin in situ	P2X7	Immunocytochemistry	Matute et al., 2007b
Stroke	Cultured oligodendrocytes	AMPA/Kainate	Blockade prevents oligodendrotoxicity	Fern and Möller, 2000
	Immature isolated optic nerve	NMDA	Blockade prevents oligodendrotoxicity	Káradottir et al., 2005; Salter and Fern, 2005; Micu et al., 2006
	Aging optic nerve	AMPA/Kainate	Blockade is protective	Baltan et al., 2008
		NMDA	Blockade is not protective	
	Oligodendrocytes and optic nerve	P2X7/pannexin-1	Receptor/hemichannel blockade	Domercq et al., 2010
	MCAO	A2A	Blockade prevents oligodendrotoxicity	Melani et al., 2009
Perinatal ischemia	Hypoxia-ischemia	AMPA and NMDA	Blockade prevents oligodendrotoxicity	Follett et al., 2004; Manning et al., 2008
	Immature optic nerve	AMPA and NMDA	Blockade prevents axon damage	Alix and Fern, 2009
	Hypoxia-ischemia plus LPS	Axon-OPC synapses	Reduced oxidative stress	Shen et al., 2012
	Hypoxia-ischemia	P2X7	Blockade prevents oligodendrotoxicity	Wang et al., 2009
	A1 receptor KO	A1	Reduced WM damage	Turner et al, 2003
Multiple sclerosis	Acute and chronic EAE	AMPA	Blockade protects myelin and axons	Kanwar et al., 2004; Pitt et al., 2000; Smith et al., 2000
	Microglia activation in optic nerve	AMPA/Kainate	Blockade prevents oligodendrotoxicity	Domercq et al., 2007
	Oligodendrocytes and optic nerve	Kainate	Blockade prevents complement attack	Alberdi et al., 2006
	Chronic EAE	A1	Absence of A1 aggravates demyelination	Tsutsui et al., 2004
	Chronic EAE	P2X7	Blockade attenuates symptoms and damage	Matute et al., 2007b
	Human brain imaging	Glutamate	Altered homeostais	Srinivasan et al., 2005
Spinal cord injury	Dorsal columns	AMPA/Kainate	Blockade attenuates damage	Li and Stys, 2000
	Contusion	P2X7	Blockade preserves function	Peng et al., 2009
	Crush	GLT-1	Lower expression increases damage	Lepore et al., 2012

EAE, experimental autoimmune encephalomyelitis; LPS, lipopolysaccharide; MCAO, middle cerebral artery occlusion; mGluR, metabotropic glutamate receptor; OPCs, oligodendrocyte precursor cells.

TABLE 2: Effects of Nonglutamatergic/Purinergic Receptor Activation in White Matter

Receptor type	Effect	Preparation	Citation
GABA-A	Axon depolarization and reduced excitability	nRON	(Constantinou and Fern, 2009; Sakatani et al., 1991, 1992; Sun and Chiu, 1999)
		Rat SCDC	(Honmou et al., 1993; Sakatani et al., 1993)
	Axon depolarization	RON	(Simmonds and Griffith, 1962)
	Oligodendrocytes and glioblasts depolarization	Neonatal mouse corpus callosum	(Berger et al., 1992)
GABA-B	Reduced activity-dependent Ca^{2+} influx into axons	nRON	(Sun and Chiu, 1999)
	Increase ischemia-tolerance	RON	(Fern et al., 1994, 1995)
Glycine	Reduced axon excitability	nRON	(Constantinou and Fern, 2009)
	Axon depolarization	RON	(Simmonds and Griffith, 1962)
Nicotinic acetylcholine receptor	Non-reversible excitability loss associated with glial pathology	nRON	(Constantinou and Fern, 2009)
	Axonal Ca^{2+} rise and reduced excitability	nRON/nMON	(Zhang et al., 2004)
Adreno-receptors	Non-reversibly excitability loss, associated with glial pathology (80 min application)	nRON	(Constantinou and Fern, 2009)
	Ischemic axon injury potentiation without affecting excitability	Rat spinal cord	(Nikolaeva et al., 2009)
	Reversible increased excitability (~10 min application)	RON/SCDC	(Honmou and Young, 1995)
	α-receptor functionally coupled to axonal G protein	Neonatal rat white matter	(Sanders et al., 2005; Venugopalan et al., 2006)
5-HT	Modulation of axonal excitability	Neonatal rat SCDC	(Saruhashi et al., 1997)
Dopamine	D1 receptors functionally coupled to G protein	Rat spinal cord	(Venugopalan et al., 2006)

nRON = neonatal rat optic nerve, RON = mature rat optic nerve, MON= mouse optic nerve SCDC = spinal dorsal column.

expression *in situ* using established cell markers. In addition to distinguishing types of glia, a reliable test for cell identification is essential due to the presence of neuronal populations in some WM structures (von Engelhardt et al., 2011), although this is not true for the commonly used optic nerve preparations.

Since the 1990s, it has been shown in a number of neonatal rodent WM preparations that glia showed Ca^{2+} rises in response to a wide range of neurotransmitters, including adenosine, ATP, glutamate, histamine, GABA, norepinephrine, serotonin, angiotensin II, bradykinin, and substance P (Bernstein et al., 1996; Kriegler and Chiu, 1993). In addition, electrophysiological criteria have been used to distinguish glial cell types, allowing the first descriptions of functional glutamate, GABA-A and glycine receptors in identified astrocytes, oligodendrocytes, glioblasts and OPCs *in situ* (Berger et al., 1992; Butt and Jennings 1994; Pastor et al., 1995). However, in the intact tissue it is often difficult to distinguish between direct and indirect effects. For example, activation of adreno-receptors can be damaging to axonal function and glial ultrastructure (Constantinou and Fern, 2009), but it is not clear whether the functional receptors are on the glia or axons, or both. Several studies have attempted to address this question by measuring changes in WM axon excitability and membrane potentials. For example, the effects of GABA-A receptor activation are associated with elevated extracellular $[K^+]$ that may originate from glia, but experimentally elevating $[K^+]$ does not duplicate the effects of GABA upon excitability leading to the conclusion that receptor expression is axonal (Sakatani et al., 1994). In general, it may be assumed that the effects of neurotransmitters on glial Ca^{2+} and membrane properties appear to be mediated largely by glial expression of neurotransmitter receptors (Butt and Jennings, 1994; Hamilton et al., 2008), whereas effects upon axonal excitability appear to be mediated largely by axolemma expression, rather than

TABLE 3: *In Situ* Expression of Nonglutamatergic/Purinergic Receptors in White Matter Glia

	Neurotransmitter	Receptor type	Preparation	Citation
Astrocytes	5-HT	5-HT2A	Rat spinal cord	(Maxishima et al., 2001)
		5-HT1A	Primate spinal and cortical WM	(Azmitia et al., 1996)
	GABA	GABA-A	Neonatal rat spinal cord WM	(Pastor et al., 1995)
		GABA-A obligatory β1 subunit	Cat cortical WM	(Rosier et al., 1993)
		GABA-A depolarization; no effect of GABA-B	nRON	(Butt and Jennings, 1994)
		GABA-A	Neonatal rat spinal cord WM	(Pastor et al., 1995)
	Glycine		Neonatal rat spinal cord WM	(Pastor et al., 1995)
	Nor-adrenaline	β2	Rat, rabbit, and human ON	(Mantyh et al., 1995)
		α2a	Adult rat SCDC	(Nikolaeva et al., 2009)
Oligodendrocytes	5-HT	5-HT2A	Rat spinal cord	(Maxishima et al., 2001)
	GABA	GABA-A	Neonatal rat spinal cord WM	(Pastor et al., 1995)
		GABA-A depolarization	MON	(Butt and Tutton, 1992)
		GABA-A patch-clamp	Neonatal mouse WM	(Berger et al., 1992)
		Some GABA-B immunoreactivity in O4+ cells	Neonatal mouse WM	(Luyt et al., 2007)
		GABA-B subtypes immunoreactivity absent from MBP+ cells (but present in axons)	Adult rat spinal cord	(Charles et al., 2003)
		General immunoreactivity of GABA-B+ cells	Rat white matter	(Charles et al., 2001; Margeta-Mitrovic et al., 1999)
	Glycine	Patch-clamp	Neonatal rat spinal cord WM	(Pastor et al., 1995)
		Glycine responses in myelin via NMDA receptors	CNS myelin	(Pina-Crespo et al., 2010)
	Dopamine	D3 on cell somata, but not co-stained	CC mouse	

nRON = neonatal rat optic nerve, ON = optic nerve; SCDC = spinal dorsal column.

glial responses that subsequently modify excitability (Nikolaeva et al., 2009; Sun and Chiu, 1999; Zhang et al., 2004).

WM Synapses and Mechanisms of Neurotransmitter Release

The old dogma that chemical synaptic specializations occur exclusively between neurons was overturned by the discovery of functional glutamatergic and GABAergic synapses between axon terminals and OPCs in the hippocampus (Bergles et al., 2000; Lin and Bergles, 2004). Notably, OPC in WM also make occasional synapses with unmyelinated axons in an *en passant* fashion (Etxeberria et al., 2010; Kukley et al., 2007; Mangin and Gallo, 2011; Ziskin et al., 2007). Indeed, pre-myelinated WM axons contain glutamate-laden vesicles and the machinery for vesicular release (Alix et al., 2008), although it is unclear whether this mechanism persists after maturation. Thus, action potentials induce vesicular release of glutamate (and possibly other neurotransmitters) from unmyelinated axons in the corpus callosum and optic nerve that activate AMPA-type glutamate receptors on OPC. In addition, action potentials evoke Ca^{2+} signals in astrocytes and OPC in the optic nerve, most likely involving the release of glutamate from axons that triggers the subsequent release

of ATP from astrocytes, involving a staggering array of ionotropic and metabotropic glutamate and purine (ATP) receptors (Hamilton et al., 2008, 2010). To add to this complex mosaic of signaling, axoglial synapses may also be modulated by the vesicular release of glutamate and/or ATP from astrocytes, as observed in classical neuron-to-neuron synapses (Volterra and Meldolesi, 2005). Furthermore, OPC may also express synaptophysin indicating they may have mechanisms for transmitting as well as receiving signals (Hamilton et al., 2010). In addition to vesicles, reversed uptake through transporters has been described for glia and is equally possible for axons (see below), and multiple potential mechanisms for neurotransmitter release from astrocytes include gap junctions, pannexins, P2X7 receptors, anion channels and stretch-activated receptors (Parpura et al., 2004). Hence, WM axons and glia have the potential for neurotransmitter release both at axoglial "synapses" and by the less specific mechanism of volume or "spillover" transmission through neurotransmitter release into the extracellular space.

Glutamate Signaling in WM

Glutamate Receptor Subtypes

Glutamate acts via ionotropic receptors (iGluR), which gate membrane ion channels permeable to cations, and metabotropic receptors (mGluR), seven transmembrane (7TM) receptors that are coupled to G proteins (for reviews, see Mayer, 2005; Swanson et al., 2005). Functional AMPA (alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptors are composed of GluA1-4 subunits, whereas kainate receptors are composed of GluK1–5 subunits. Similarly, NMDA (*N*-methyl-D-aspartate) receptors consist of a GluN1 subunit, together with GluN2A-D subunits and/or GluN3A-B. In turn, mGluRs are classified as group I (mGluR1, mGluR5), group II (mGluR2, mGluR3) and group III (mGluR4, mGluR6–8) 7TM receptors. Glia express functional iGluR and mGluR in both GM and WM (for recent reviews, see (Bakiri et al., 2009; Matute, 2011). In particular, astrocytes of the optic nerve have been shown to respond to glutamate acting on both AMPA- and NMDA-type receptors, as well as on group I mGluR, to induce an increase in astroglial $[Ca^{2+}]_i$, which leads to the release of ATP by a mechanism involving P2X7 receptors (Hamilton et al., 2008). Similarly, oligodendrocytes have been shown to express in their somata functional AMPA and kainate type receptors throughout a wide range of developmental stages and species, including humans (Matute et al., 2007a). In addition, immature and mature oligodendrocytes express in their processes NMDA receptors, which can be activated during injury (Baltan et al., 2008; Karadottir et al., 2005; Micu et al., 2006; Salter and Fern, 2005). Moreover, oligodendrocytes also express receptors from all three groups of mGluR, although the expression level of these receptors appears to be developmentally regulated and is reported to be very low in mature oligodendrocytes (Deng et al., 2004). In turn, WM OPCs express AMPA-type glutamate receptors which can be activated by glutamate released from mechanically activated astrocytes and from axons during action potential passage (Hamilton et al., 2010; Kukley et al., 2007; Ziskin et al., 2007). In contrast, little is known about glutamate receptors in WM microglia, although glutamate is involved in the transmission of death signals to microglia, to which they respond by migrating to sites of neuronal injury (Sieger et al., 2012). In GM, ramified microglia may express AMPA and mGluR which can promote inflammation, chemotaxis, neuroprotection or neurotoxicity (for reviews see Domercq et al., 2013; Pocock and Kettenmann, 2007).

Glutamate Homeostasis

Glutamate uptake from the extracellular space is conducted by specific glutamate transporters (GluT), and is essential for the shaping of excitatory postsynaptic currents and for the prevention of excitotoxic death due to overstimulation of glutamate receptors (Rothstein et al., 1996). At least five glutamate transporters have been cloned (Danbolt 2001), and of these, GLT-1 (glutamate transporter 1, also known as EAAT2—excitatory amino acid transporter 2) exhibits the highest level of adult expression, overwhelmingly in astrocytes, and is responsible for most glutamate transport. GluTs are also expressed by oligodendrocytes, although their expression has been less well characterized than in astrocytes. The main transporter expressed by oligodendrocytes is GLAST (glutamate aspartate transporter; also known as EAAT1). The neuronal transporter, termed EAAC1 (excitatory amino acid carrier 1, or EAAT3), is present in a subpopulation of adult OPCs (Domercq et al., 1999). It appears that all WM macroglial cells differentially express the three major GluTs. These transporters maintain basal levels of extracellular glutamate in the range of 1 to 2 μM and prevent over-activation of glutamate receptors under physiological conditions. In turn, GluT can contribute to glutamate release in WM by reversing Na^+-dependent glutamate uptake in injured axons that suffer internal Na^+ overload that reverses GluTs (Domercq et al., 1999; Li et al., 1999; Longuemare et al., 1999). Moreover, given the rising prominence of NMDA receptors in WM, and that glycine is an obligatory co-agonist, it is important to note that glycine transporters GLYT1/GLYT2 are expressed in WM (Borowsky et al., 1993), and their activity will influence the effects of glutamate signaling.

In addition, glutamate homeostasis is also regulated by system x_c^-, a membrane-bound, Cl^--dependent, Na^+-independent antiporter that mediates the cellular uptake of cystine in a 1:1 exchange for glutamate (Conrad and Sato, 2012).

The cystine/glutamate antiporter is the main neuronal source of cystine, which is intracellularly converted to cysteine, the rate-limiting substrate in glutathione synthesis. System x_c^- is vital for antioxidant defence; its expression is rapidly upregulated under oxidative stress, although its enhanced function increases extracellular glutamate levels and may cause excitotoxicity (Conrad and Sato, 2012). Notably, system x_c^- is expressed by astrocytes, and by resting and activated microglia (Domercq et al., 2007; Had-Aissouni, 2012; Pampliega et al., 2011).

Glutamate Signaling in Axons

Axons are also endowed with glutamate receptors and glutamate transporters. Native AMPA receptors in axons are formed by the GluA4 subunit and kainate receptors are composed of at least GluK1 and GluK2 subunits, which in all instances are located in the internodes (Ouardouz et al., 2009a,b). In turn, the major glutamate transporter expressed by axons is GLT-1, although significant levels of GLAST are also present (Li et al., 1999). Axonal AMPA receptors in spinal axons are weakly permeable to Ca^{2+}, the entry of which releases additional Ca^{2+} from the axonal endoplasmic reticulum (ER) by opening intracellular Ca^{2+} channels known as ryanodine receptors—RyR (Ouardouz et al., 2009b). In contrast, axonal kainate receptors with the GluK1 subunit are coupled to phospholipase C (PLC) activation (Ouardouz et al., 2009b). In addition, activation of kainate receptors with the GluK2 subunit induces a small amount of Ca^{2+} entry that stimulates nitric oxide synthase (NOS), as well as a local depolarization that activates L-type Ca^{2+} channels, and subsequently RyR in the axoplasmic reticulum (Ouardouz et al., 2009a). The functional significance of these signaling mechanisms by glutamate receptors in axons is unclear, although they may serve to amplify axonal Ca^{2+} signals that appear to be weak because of the limited quantity of cation available in the narrow peri-axonal space (Ouardouz et al., 2009a). Notably, local activation of axonal AMPA/kainate receptors by glutamate released from periaxonal astrocytes may increase the width of action potentials while they travel down unmyelinated GM axons in the hippocampus (Sasaki et al., 2011). In turn, the broadened action potential triggers larger calcium elevations in presynaptic boutons and facilitates synaptic transmission to postsynaptic neurons (Sasaki et al., 2011). This glial-mediated action potential modification might enable axonal computation through the geometry of axon wiring.

Glutamate Signaling in Oligodendrocytes and Myelin

Glutamate signaling in oligodendrocytes is also relevant to myelination. Action potentials traveling along axons can release glutamate in a vesicular manner, which promotes myelin induction by stimulating the formation of cholesterol-rich signaling domains between oligodendrocytes and axons and increasing the local synthesis of major myelin proteins (Wake et al., 2011). Mature CNS myelin sheaths express various AMPA and kainate receptor subunits, as well as functional NMDA receptors (reviewed in Stys, 2011). Curiously, these NMDA receptors have unique properties: about half of them are formed by receptors containing GluN2 subunits (probably GluN1-GluN2C, D); the remaining NMDA receptors lack the GluN2 subunit and therefore, are "glycine only" receptors formed by GluN1-GluN3A subunits; and they display reduced Ca^{2+} permeability and Mg^{2+} sensitivity. Interestingly, immunogold labeling and electron microscopic examination revealed that both NMDA receptors are preferentially localized at the inner and outer myelin loops. The presence of the apparent machinery for vesicular release in axons (Alix et al., 2008) and neurotransmitter receptors in the inner myelin loop led to the hypothesis that myelin is the target for neurotransmission across a putative axo-myelin "synapse," with the internodal axon cylinder acting as the presynaptic element and the periaxonal space equivalent to the synaptic cleft (Stys, 2011). In addition, WM possesses neurotransmitter uptake systems in the axon membrane, particularly at the nodes of Ranvier, as well as in the myelin (Stys, 2011). Together, these findings suggest that communication between axons and myelin shares many features of conventional chemical synapses found in GM. This axon-myelin interplay may provide a mechanism by which myelin-supporting oligodendrocytes increase the transfer of energy metabolites to fuel electrically active fibres (Stys, 2011). Such a system might seem at odds with evidence that glycogen (which is contained exclusively in astrocytes) supports axons during intense activity or in the temporary absence of glucose (see Hirrlinger and Nave, 2014). In fact, astrocytes and oligodendrocytes form gap junctions, and may cooperate to provide a "supply line" for the delivery of energy substrate to axons, whether they are myelinated or not (Lee et al., 2012). Although this hypothesis needs further experimental support, it provides novel ideas that may be relevant to myelination and WM damage.

In addition to oligodendrocytes, activation of glutamatergic synapses in OPCs induces Ca^{2+} entry, either directly through the receptor channel or indirectly though Na^+ entry and depolarization resulting in activation of voltage-dependent calcium channels and/or the reversal of Na^+/Ca^{2+}-exchanger (reviewed by Mangin and Gallo, 2011). Neuron-OPC synapses are formed during spontaneous remyelination after demyelination, a feature suggesting that they may act in the early steps of the myelination/remyelination process (Etxeberria et al., 2010). This possibility is supported by the fact that OPC lose their synapses as they differentiate

into myelinating oligodendrocytes (Kukley et al., 2010). Therefore, it is plausible that glutamatergic synapses inhibit OPC proliferation in an activity-dependent manner (Mangin and Gallo, 2011). Indeed, there is evidence that glutamate inhibits OPC proliferation, increases their migration speed, and inhibits their ability to differentiate into oligodendrocytes *in vitro* (reviewed in (Mangin and Gallo, 2011). In apparent contradiction with this idea, recent data support the notion that glutamate acting at NMDA receptors may contribute to oligodendrocyte maturation (Cavaliere et al., 2012).

Despite this wealth of information, direct evidence that oligodendroglial glutamate receptors have a physiological role in regulating myelination *in vivo* is lacking.

Glutamate Signaling in WM Injury and Repair

Glutamate and Excitotoxicity. The term excitotoxicity was coined more than 50 years ago, and refers to neuronal damage by excessive activation of glutamate ionotropic receptors. Excitotoxicity is also highly relevant to WM damage, where receptor-mediated glutamate toxicity is clearly involved in certain pathological conditions (Matute 2011; Ransom and Baltan 2009). Over-activation of AMPA and kainate receptors causes oligodendrocyte death and primary and/or secondary myelin destruction (Matute 2011). The influx of Ca^{2+} upon receptor activation and the ensuing accumulation of Ca^{2+} within mitochondria are central to this process. These events lead to mitochondrial depolarization, increased production of radical oxygen species, and the release of pro-apoptotic factors, which in turn activate caspase-dependent and -independent oligodendrocyte death (Sanchez-Gomez et al., 2003). Detailed studies of oligodendrocyte excitotoxicity have shown that Bax and calpain are essential intermediaries (Sánchez-Gómez et al., 2011), and that Ca^{2+}-induced calcium release through RyR also contributes to mitochondrial dysfunction and ER stress (Ruiz et al., 2010). However, the mechanisms triggered by NMDA receptor-mediated insults to oligodendrocytes have not yet been studied in detail.

The direct inhibition of glutamate uptake in axonal tracts leads to oligodendroglial loss, massive demyelination, and severe axonal damage (Domercq et al., 2005). Other factors that may contribute to perturbing glutamate homeostasis and cause WM damage include: altered activity of the glutamate-producing enzyme glutaminase in activated macrophages/microglia in close proximity to dystrophic axons (Werner et al., 2001); and reduced expression of the glutamate transporters GLAST and GLT-1 in oligodendrocytes as a consequence of enhanced exposure to the proinflammatory cytokine tumour necrosis factor α (Pitt et al., 2003) and oxidative stress (Domercq et al., 2007). Moreover, activated microglia increase their own expression of xCT (glutamate-cystine exchange transporter), which contributes further to increasing glutamate levels and glutamate toxicity (Domercq et al., 2007). In turn, excessive activation of internodal axonal glutamate receptors may induce the release of substantial amounts of calcium from axoplasmic ER and activate calcium-dependent enzymes that ultimately ignite the collapse of the axon (Stirling and Stys, 2010).

Glutamate and Ischemia. Damage of central WM is a major cause of functional disability in cerebrovascular disease. Injury to WM as a consequence of hypoxic-ischemic injury occurs in periventricular leukomalacia (PVL) in neonates and in stroke and cardiac arrest in adults, as well as in vascular dementia in the aging brain. The metabolic rate of WM is only modestly lower than that of GM, and animal studies suggest that WM can be damaged by even brief ischemia (Pantoni et al., 1996). Ischemic insults typically result in transmembrane ion gradient breakdown and membrane depolarization, leading ultimately to toxic intracellular Ca^{2+} overload. The final stage is the activation of Ca^{2+}-dependent enzymes (e.g. calpains, phospholipases, and other enzymes), resulting in irreversible damage of WM glia and axons (Hamner et al., 2011; Stys et al., 1992; Tsutsui and Stys, 2013).

Glutamate excitotoxicity contributes to WM demise during ischemia and putative subsequent reperfusion. Immature and differentiated oligodendrocytes are very sensitive to transient oxygen and glucose deprivation (Fern and Moller, 2000). Both cell types can be partially protected from irreversible ischemic injury by reducing extracellular Ca^{2+} or by AMPA/kainate receptor antagonists, but not by the blockade of Ca^{2+} influx through Ca^{2+} voltage-dependent channels or Na^{+}/Ca^{2+}exchanger, which suggests that Ca^{2+} entry through the receptor channel is sufficient to initiate cell demise. Notably, simulated ischemia in young animals induces an inward current in oligodendrocytes that is partly mediated by NMDA and AMPA/kainate receptors (Karadottir et al., 2005), and which is directly toxic to the cell processes (Salter and Fern, 2005). In addition, Ca^{2+} levels also increase in myelin itself during ischemia (an effect that is abolished by broad-spectrum NMDA receptor antagonists), causing ultrastructural damage to the myelin sheath (Micu et al., 2006).

WM becomes intrinsically more vulnerable to ischemia with age and the mechanisms of glutamate-mediated damage change (Baltan et al., 2008). Thus, ischemic WM injury in older mice is predominately mediated by glutamate release through reverse glutamate transport (probably from astrocytes) and the ensuing activation of AMPA/kainate-type glutamate receptors (Baltan et al., 2008). Intriguingly, blockade of NMDA receptors aggravates the outcome of ischemia in older

animals (Baltan et al., 2008), a feature which may have to do with a potential role of these receptors in energy support.

Perinatal Ischemia. PVL is the major neuropathological lesion in premature infants, and involves focal WM necrosis and subsequent hypomyelination. The pathophysiology of PVL is multifactorial and includes hypoxia-ischemia−induced glutamate excitotoxicity, oxidative stress, and inflammation (Volpe, 2009) (see Back and Rosenberg, 2014). Injury to OPCs caused in part by glutamate contributes to the pathogenesis of myelination disturbances in PVL (Back and Rivkees, 2004). In the immature human brain, the susceptibility of developing oligodendrocytes to hypoxia-ischemia correlates with their expression of glutamate receptors of the AMPA receptor subtype (Talos et al., 2006), and systemic administration of AMPA receptor antagonists attenuates injury in a rat model of PVL (Follett et al., 2004). In addition, developing oligodendrocytes also express NMDA receptors; their blockade with memantine attenuates oligodendrocyte loss and prevents the long-term reduction in cerebral mantle thickness that is observed in experimental PVL (Manning et al., 2008). Intriguingly, synapses between axons and OPCs are quickly and profoundly damaged in PVL models, an observation that outlines the relevance of these synaptic contacts to WM integrity during development (Shen et al., 2012).

Ischemic injury to axons is also a feature of PVL; it occurs early in local and diffuse damage associated with this pathology (Haynes et al., 2008). Interestingly, experimental ischemia in immature axons produces action potential failure and focal breakdown of the axolemma of small premyelinated axons at sites of contact with oligodendrocytic processes, which are also disrupted (Alix and Fern 2009). Axon damage is prevented by NMDA and AMPA/kainate receptor blockers, suggesting that glutamate receptor-mediated injury to oligodendrocytic processes in contact with premyelinated axons precedes disruption of the underlying axon and/or that premyelinated axons also express GluRs (Alix and Fern, 2009).

Multiple Sclerosis. The major demyelinating disease of the CNS is MS, which is the foremost disabling pathology among young adults (Lassmann, 2014). MS is a chronic, degenerative disease that is characterized by focal lesions with inflammation, demyelination, infiltration of immune cells, oligodendrocyte death, and axonal degeneration (Prineas et al., 2001). It is widely accepted that the aetiology of this illness has autoimmune and inflammatory grounds, and that a derailment of the immune system leads to cell- and antibody-mediated attacks on myelin. Both genetic and environmental factors contribute to MS susceptibility (Zamvil and Steinman, 2003). Among them, primary and/or secondary alterations in glutamate signaling cause excitotoxicity, which in turn contributes to MS pathology. Numerous studies conducted in cellular and animal models of MS, as well as in post-mortem brain and in patients, have indicated that excitotoxicity mediated by Ca^{2+}-permeable glutamate receptors contributes to oligodendrocyte death, demyelination, and tissue damage (Matute et al., 2001; Srinivasan et al., 2005; Vallejo-Illarramendi et al., 2006). In particular, experimental autoimmune encephalomyelitis (EAE), a mouse disease model that exhibits clinical and pathological features of MS, is alleviated by AMPA and kainate receptor antagonists (Pitt et al., 2000; Smith et al., 2000). In contrast, blockade of NMDA receptors with MK-801 does not attenuate chronic EAE symptoms (Matute, 2010), and conditional deletion of GluN1 in oligodendrocytes does not alter the onset and course of symptoms in this experimental model of MS (Guo et al., 2012; but see Graselli et al., 2013). Remarkably, blockade of these receptors in combination with anti-inflammatory agents is effective even at an advanced stage of unremitting EAE, as assessed by increased oligodendrocyte survival and remyelination, and corresponding decreased paralysis, inflammation, CNS apoptosis, and axonal damage (Kanwar et al., 2004). Importantly, a recent genome-wide association screening study identified associated alleles in AMPA receptor genes in MS patients who exhibited the highest levels of glutamate and brain volume loss (Baranzini et al., 2010). These findings provided a novel quantitative endophenotype that may help clarify the pathophysiology of the heterogeneity of clinical expression in MS.

Glutamate levels are increased in the human MS brain (Srinivasan et al., 2005) as a consequence of reduced expression of the glutamate transporters GLAST and GLT-1 (Pampliega et al., 2008; Vallejo-Illarramendi et al., 2006). Another mechanism accounting for glutamate dyshomeostasis is genetic variability in the promoter of the major glutamate transporter, GLT-1, which results in lower transporter expression (Pampliega et al., 2008). In turn, upregulation of xCT in the monocyte-macrophage-microglia lineage is associated with immune activation in both MS and EAE (Pampliega et al., 2011).

Non-toxic glutamate concentrations also contribute to demyelinating pathology by inducing oligodendrocyte death by sensitizing oligodendrocytes to complement attack (Alberdi et al., 2006). Intriguingly, complement toxicity is induced by the activation of kainate, but not of AMPA, NMDA, or metabotropic glutamate receptors. Oligodendrocyte death by complement requires the formation of the membrane attack complex, which in turn increases membrane conductance and induces Ca^{2+} overload and mitochondrial depolarization, as well as an increase in the level of reactive oxygen species (Alberdi et al., 2006). Sensitization by glutamate to complement attack may initiate MS lesions with massive oligodendrocyte apoptosis (Barnett and Prineas, 2004).

Physical Trauma. Traumatic injury to the CNS inevitably involves damage to WM and causes primary mechanical destruction of glia and axons (Kou and VandeVord, 2014). In addition, secondary impairment of tissue occurs as a consequence of a prolonged pathological response involving chronic inflammation, microglial activation, and astroglial scar formation. This prolonged response can ultimately result in the development of a large cavity at the site of the lesion and persistent functional deficits (Dumont et al., 2001). Tissue destruction after traumatic brain injury leads to the release of large amounts of glutamate, which cause Ca^{2+}-dependent excitotoxic damage to white matter astrocytes, oligodendrocytes, and myelin, but not to axons (Li and Stys, 2000). Indeed, glutamate dysregulation is centrally involved in the outcome following traumatic spinal cord injury. After thoracic crush of the spinal cord, mice heterozygous for the astrocytic glutamate transporter GLT-1 exhibit attenuated recovery of hindlimb motor function, increased lesion size, and reduced tissue sparing (Lepore et al., 2011). These findings indicate that glutamate uptake by astrocytes limits secondary damage after CNS traumatic injury, and that promoting glutamate transporter expression and function may favor postlesion recovery.

Purine Signaling in WM

Purine Receptors

Glial cells express multiple purine receptors (Butt, 2011). Adenosine acts via four subtypes of G-protein coupled receptors (A1 and A3 receptors inhibit cAMP via Gi/o, whereas A2A and A2B receptors stimulate cAMP via Gs), and all have been described in astrocytes, OPC and microglia, but they appear to be downregulated in differentiated oligodendrocytes (Abbracchio et al., 2009; Ciccarelli et al., 2001; Stevens et al., 2002). Adenosine receptors mediate the repulsive effects of ATP/adenosine on microglia (Gyoneva et al., 2009), evoke Ca^{2+} signals in optic nerve astrocytes and probably OPC *in situ* (Hamilton et al., 2008), and regulate OPC differentiation and myelination (Stevens et al., 2002). Immunocytochemical evidence for A1 receptors has been reported in adult rat corpus callosum axons and their activation modulated axon conduction (Swanson et al., 1998). Otherwise, there is little direct knowledge of the normal physiological functions for adenosine receptors in WM. Adenosine is very important in pathology, since its levels increase rapidly with tissue ischemia and inflammation. Adenosine receptors contribute to WM injury in the preterm infant by altering oligodendrocyte development and are therapeutic targets in stroke and MS (Matute, 2011; Matute et al., 2012; Rissanen et al., 2013; Rivkees and Wendler, 2011).

A key feature of glia throughout the CNS is their expression of functional ionotropic P2X and metabotropic P2Y receptors, which are the substrate for glial Ca^{2+} signaling (James and Butt, 2002). P2X receptors comprise seven subtypes (P2X1–7), which are ligand-gated channels permeable to Na^+, K^+ and Ca^{2+} (Burnstock, 2007). Glia may express all P2X subtypes, but P2X1-P2X4 and P2X7 may predominate in astrocytes (Ashour and Deuchars, 2004; Franke et al., 2001; Kanjhan et al., 1999; Loesch and Burnstock, 1998), oligodendrocytes and OPCs (Agresti et al., 2005a,b; Matute et al., 2007), and microglia (Franke et al., 2004; Tsuda et al., 2003). There is direct immunohistochemical evidence of P2X7 receptors in oligodendrocytes *in vivo*, and they have been shown to mediate raised $[Ca^{2+}]_i$ in WM astrocytes *in situ* and oligodendrocytes *in vitro* (Hamilton et al., 2008, 2010; James and Butt, 2001; Matute et al., 2007b). The P2X7 receptor subtype is capable of pore formation, resulting in sustained influx of Ca^{2+} and mediates glial pathological responses, in particular the loss of oligodendrocytes and myelin in ischemia and demyelination (Domercq et al., 2010; Matute and Cavaliere, 2011; Matute et al., 2007b). Interestingly, a decrease in P2X7 receptor expression has been reported in cultured OPCs and subcortical white matter in a hypoxic-ischemic injury model in postnatal rats (Wang et al., 2009), although the pathophysiological significance of these observations is unclear. Microglia have also been shown to express P2X4 receptors in the developing corpus callosum, where they have a role in inducing activation during ischemia, but their expression was markedly downregulated postnatally (Li et al., 2011).

P2Y are 7TM receptors and eight subtypes have been cloned in mammals, with differential sensitivities to the adenine nucleotides ATP/ADP (P2Y1,11,12,13), the uracil nucleotides UTP/UDP (P2Y4,6), the adenine and uracil nucleotides (P2Y2), and UDP-glucose (P2Y14). All P2Y receptors are G-protein-coupled and activate phospholipase C (PLC)/inositol triphosphate (InsP3) and Ca^{2+}-release from the smooth ER via Galpha(q/11) (P2Y1, P2Y2, P2Y4, P2Y6, and P2Y11), or regulate adenylyl cyclase via Galpha(s) and Galpha (i/o) proteins (P2Y12, P2Y13, and P2Y14) (Burnstock 2007). P2Y receptors are broadly distributed in glia, although the specific subtypes expressed in WM are less clearly defined (James and Butt, 2002). Prominent immunolabeling for P2Y1 receptors has been demonstrated in WM oligodendrocytes and astrocytes (Moran-Jimenez and Matute, 2000) and they are the primary receptors involved in ATP-mediated Ca^{2+} signals in optic nerve astrocytes and most likely oligodendrocytes and OPCs *in situ* (Hamilton et al., 2008, 2010; James and Butt, 2002). In OPCs, P2Y1 receptor activation *in vitro* stimulates cell migration and development (Agresti et al., 2005). Notably, P2Y12 receptors are enriched in oligodendrocytes and are involved in demyelination and MS (Amadio et al., 2006, 2010). The P2Y-like receptor

GPR17 is highly expressed in OPCs and mediates their response to uracil nucleotides (e.g. UDP-glucose) and cysteinyl-leukotrienes (e.g. LTD4 and LTC4), which may be important during development and injury (Boda et al., 2011; Fumagalli et al., 2011). GPR17 is increased in animal models of ischemia and trauma, as well as human traumatic brain injury, where it may mediate microgliosis, as well as adenine nucleotide-induced cytotoxicity of OPCs (Ceruti et al., 2009, 2011; Franke et al., 2013; Zhao et al., 2011).

Mechanisms for ATP Release in WM

Studies by the Butt and Matute groups have demonstrated ATP mediates raised Ca^{2+} in optic nerve astrocytes *in situ* via a wide range of receptors (see above) and that oligodendrocytes at least *in vitro* respond in the same way. The primary source of endogenous ATP in WM is not resolved, but in the optic nerve ATP is released during action potential propagation and astrocytes release ATP following mechanical stimulation (Hamilton et al., 2008, 2010). Optic nerve astrocytes express P2X7 receptors, which are implicated in ATP release (Hamilton et al., 2008), and astrocytes widely express connexin-43, pannexin-1, and volume-regulated anion channels, which are additional potential mechanisms of neurotransmitter release in astrocytes (Parpura et al., 2004). Astrocytes may also release ATP by vesicular exocytosis (Montana et al., 2006), although there is no direct evidence for this in WM. WM axons have not been shown to release ATP, although it is conceivable they could release ATP by vesicular mechanisms either in specific vesicles or as a cotransmitter (see above for glutamate).

Physiological Functions for ATP Signaling in WM

WM astrocytes extend fine finger-like projections that form points of contact with nodes of Ranvier (Butt et al., 1994), the sites of action potential propagation and in myelinated tracts the only possible site of direct axon-to-astrocyte signaling. Axonal electrical activity triggers astrocyte calcium signals, which in turn triggers their release of ATP to propagate and amplify the initial calcium signal through the glial network (Hamilton et al., 2008, 2010). Most evidence indicates that astrocyte signaling spreads as a circular wave in all directions from a focal source, through gap junctions and by the release of ATP to activate glial receptors in a "spillover" or volume transmission manner. The ATP-mediated rise in astrocyte calcium may stimulate them to release glutamate or other neurotransmitters, such as GABA and acetylcholine (ACh) (see below), which have been shown to act on axonal receptors to modulate their conduction properties (Sakatani et al., 1994; Sasaki et al., 2011; Sun and Chiu, 1999; Zhang et al., 2004). In addition, intercellular Ca^{2+} waves in astrocytes have been shown to trigger microglial Ca^{2+} responses through the release of ATP (Schipke et al., 2002; Verderio and Matteoli, 2001), which is central to their injury response (Maeda et al., 2010; Tsuda et al., 2010). Furthermore, ATP is a potent vasoconstrictor and its metabolite adenosine is a potent vasodilator, and so their release by astrocytes at the gliovascular interface could provide a mechanism for local regulation of blood flow, both physiologically and in pathology.

There is abundant evidence that ATP mediates Ca^{2+} signals in oligodendrocytes via both P2Y1 and P2X7 receptor subtypes (Alberdi et al., 2005; James and Butt, 2001; Kirischuk et al., 1995). Activation of P2X7 receptors can result in demyelination and the loss of oligodendrocytes and may have a particular role in pathological conditions such as ischemia and MS (see below). Direct evidence of a physiological role for ATP signaling in oligodendrocytes is lacking, due to the difficulty of calcium imaging from oligodendrocytes *in situ* and distinguishing between direct and indirect actions of any stimulus, but it seems inconceivable that ATP released by astrocytes and during axonal action potential propagation would not activate these receptors on oligodendrocytes. It is reasonable to conclude that ATP-mediated signaling is physiologically important in oligodendrocytes, possibly as a communications pathway by which axonal activity helps maintains myelin production by oligodendrocytes, in a way similar to that described in developing WM (Ishibashi et al., 2006; Stevens et al., 2002; Wake et al., 2011).

ATP and Adenosine Mediate Axonal Control of Myelination

OPCs form intimate contacts with axons at presumptive "synapses" and at nodes of Ranvier in unmyelinated and myelinated axons (Butt et al., 1999; Hamilton et al., 2010; Ziskin et al., 2007), and respond by raised intracellular calcium to ATP and adenosine released during axonal electrical activity (Hamilton et al., 2010; Stevens et al., 2002). *In situ* studies indicate adenosine acts to inhibit OPC proliferation and promote their differentiation and myelination (Stevens et al., 2002), whereas ATP acts on astrocytes to trigger the release of leukemia inhibitory factor (LIF), which in turn acts on oligodendrocytes to promote myelination (Ishibashi et al., 2006). In addition, there is evidence in culture that adenosine acting via A1 receptors and ATP acting via P2Y1 and P2X7 receptors regulate the migration, proliferation and differentiation of OPCs (Agresti et al., 2005; Othman et al., 2003). As noted above for glutamate, axonal release of ATP and/or adenosine may be important in remyelination and repair (see Franklin and Gallo, 2014), since demyelinated axons form synapses with adult-born OPCs in an experimental model of demyelination (Etxeberria et al., 2010).

Purine Receptors and WM Pathology

Adenosine, P2X, and P2Y receptors are implicated in reactive astrogliosis, demyelination and microglial activation (Matute

and Cavaliere, 2011). The majority of studies have been on GM and these are likely to inform on processes in WM, but in general direct experimental evidence in WM is lacking. As noted above, adenosine and P2X7 receptors are implicated in oligodendrocyte/myelin loss in ischemia and MS in WM (Domercq et al., 2010; Matute and Cavaliere, 2011; Matute et al., 2007b). In GM, P2Y1, and P2Y12 receptors are involved in astrogliosis *in vivo* (Franke et al., 2001), and the P2X receptor antagonist PPADS significantly decreases astrogliosis following spinal cord injury *in vivo* (Rodriquez-Zayas et al., 2012). However, P2X4 and P2Y12 receptors also regulate the microglial injury response (Franke et al., 2013), and the latter are expressed by oligodendrocytes/myelin (Amadio et al., 2006), making it difficult to distinguish specific cellular responses *in vivo*.

Non-Glutamatergic/Purinergic Neurotransmitters in WM

As described above, there are a variety of developmental functions now understood for WM glutamatergic/purinergic receptors (Table 1), but functional receptors for GABA-A/B, glycine and to a lesser extent nicotinic, 5-HT, dopamine and adrenoreceptors have also been reported in WM, although their functions remain mysterious (Tables 2 and 3). In a recent study, Fern and colleagues found that mRNA for three quarters of receptor subunits from a panel of non-glutamatergic/purinergic receptors were robustly expressed in WM glial cells, with some found at higher levels than in GM structures (Domingues et al., 2010). It seems likely that such wide-scale expression in glia, together with strong evidence for functional expression in some axons, is physiological, possibly in the same manner as described for glutamate and ATP. However, extrapolation from studies based on GM glia should be avoided when considering WM glia; for example it has been pointed out by Bergles et al. (2010) that the GABA-A receptor currents found in OPC in GM areas have not been seen in corpus callosum using approaches that should have detected them if present (Kukley et al., 2007; Ziskin et al., 2007).

GABA and Glycine

It has been estimated that ~75% of human synapses are GABAergic (Chang et al., 2003). It is therefore surprising that MRS suggests that the GABA concentration in human WM is ~50% of that in GM, where the vast majority of known GABAergic synapses are located (Choi et al., 2007; Jensen et al., 2005). A similarly high percentage has been found for WM glycine (Banerjee et al., 2012), and biochemical analysis of adult pig brain gives values of ~50 and ~100%, respectively (Henjum and Hassel, 2007a, 2007b). Data on extracellular neurotransmitter concentrations or physiological neurotransmitter release in WM are lacking, although ischemia-induced release of neurotransmitters such as GABA has been documented (Shimada et al., 1993). GABA is localized in neonatal rat optic nerve glia, with expression down-regulated with maturation (Ochi et al., 1993; Sakatani et al., 1992), although this may be due to increased rates of GABA degradation since numerous GABA+ WM astrocytes are apparent in adult rat following inhibition of the catabolic enzyme GABA-alpha-ketoglutaric acid aminotransferase (Bull and Blomqvist, 1991). High concentrations of neurotransmitter such as GABA and glycine are also present in a sub-population of mature WM axons in several species (Carlton et al., 1996; Davanger et al., 1991; Rogers and Pow, 1995; Todd and Sullivan, 1990; van den Pol and Gorcs, 1988; Wilson et al., 1996).

Block of GABA uptake mimics the effects of GABA upon axon conduction in the neonatal rat optic nerve (Sakatani et al., 1991), while block of catecholamine uptake mimics the effect of nor-adrenaline (Nikolaeva et al., 2009); observations consistent with tonic operation of functional neurotransmitter uptake in the tissue. mRNA for GAT 1–3 GABA transporters is present in neonatal and adult rat optic nerve (Howd et al., 1997), while protein expression levels for GAT-2 are high in subcortical adult rat WM (Conti et al., 1999). GAT-1 protein expression is absent from monkey and human adult optic nerve (Casini et al., 2006), but expression can be robust in axons of several WM structures in rat and man, with no apparent expression in accompanying glia (Conti et al., 1998; Minelli et al., 1995; Yan and Ribak, 1998). Several other studies report low or zero GAT expression in various rat WM structures (e.g. Durkin et al., 1995; Itouji et al., 1996), although species differences may be significant with high levels of GAT-3 expression reported in oligodendrocytes in cat, monkey and man (see Pow et al., 2005). Glycine transporters GLYT1/GLYT2 are expressed in WM (Borowsky et al., 1993), including glial cells in rat spinal cord WM (Zafra et al., 1995). GABA and glycine uptake rates in adult pig WM proteoliposomes approach ~20% and ~100% of the comparable levels in GM respectively, and are sensitive to selective inhibitors (Henjum and Hassel, 2007a, 2007b).

There is therefore strong evidence for GABA and glycine in WM axons and glia and functional neurotransmitter uptake into WM glia both in the neonate and the adult, but species and regional variations appear to be quite significant. In light of these observations, it is interesting that vigabatrin, a GABA elevator in clinical practice as an anti-epileptic, can produce selective WM toxicity involving myelin splitting (see Walzer et al., 2011). Elevated glycine levels due to genetic mutations are also associated with a variety of WM pathologies (de Koning et al., 2000; Press et al., 1989; van der Knaap et al., 1999). Such observations highlight the clinical relevance of non-glutamatergic/purinergic WM neurotransmitters, and confirm functional uptake in the tissue; the actions of glycine may be primarily via NMDA receptors (see above), and so it can be considered an element of glutamatergic signaling.

Other Neurotransmitters

There is less information regarding adreno-receptors, nicotinic cholinergic, dopaminergic and serotonergic receptors in WM than for GABA and glycine. Nicotinic agonists are protective against injury in developing WM, having complex actions via several receptor types (Laudenbach et al., 2002; Paris et al., 2006). Expression of the α2 receptor is widespread in developing WM structures in rat, but declines to low levels in adult (Happe et al., 2004); expression is functional being associated with elevated GTPγS binding indicative of G-protein stimulation (Sanders et al., 2005). There is good evidence for trafficking of various nicotinic receptor proteins along optic nerve axons (Cox et al., 2008) and nicotinic receptor binding is particularly high in human and non-human primate WM structures such as sub-cortical WM (Ding et al., 2004). Serotonin has been seen in adult monkey WM axons (Westlund et al., 1992), and receptor expression reported in adult rat spinal cord WM astrocytes (Maxishima et al., 2001). The functional significance of these observations is not clear. In addition, α1 and β2 adreno-receptors have been described in the rabbit, rat, and human optic nerve, and β2 receptors are up regulated after optic nerve transection (Mantyh et al., 1995). β2 receptors are present in GFAP+ astrocytes in normal appearing WM from MS patients, but appears to be lost in plaques (De Keyser et al., 1999, 2001, 2004). This may have significant consequences for disease progression by either affecting immunoresponses or disruption of white matter energy metabolism (Cambron et al., 2012). Dopamine and noradrenaline can evoke physiological responses in rat spinal cord WM via D1 or α1/α2/β adreno-receptors respectively, and there is some evidence for low levels of D1 receptor expression in human WM (Sovago et al., 2005; Venugopalan et al., 2006). Catecholamines can influence ischemic injury in adult WM and are toxic to developing WM (Constantinou and Fern, 2009; Nikolaeva et al., 2009); the role of neurotransmitters in WM pathology is covered in a companion review in this volume.

Physiological Functions of Nonglutamatergic/Purinergic Neurotransmitter Systems in WM

We have summarized data consistent with WM expression of a number of non-glutamatergic/purinergic neurotransmitter systems in Tables 2 and 3. In general, developing WM axons express a wide range of receptors and their activation results in axonal depolarization and reduces excitability. Immunostaining and PCR confirm expression of multiple receptor types in *in vivo* in astrocytes and oligodendrocytes, and functional electrophysiological and imaging studies suggest they may be developmentally regulated. A number of functional glial uptake mechanisms have also been convincingly reported. To date, it has not been possible to specifically target WM and so it remains speculative as to why WM contain such varied neurotransmitter signaling mechanisms. Most of these neurotransmitters have been shown to affect OPCs and their differentiation in one manner or other: for example, activation of GABA-AR inhibits proliferation in the early oligodendroglial lineage (Yuan et al., 1998), whereas mAChR activation significantly increases OPC proliferation and inhibits their differentiation into myelinating oligodendrocytes (De Angelis et al., 2011). An alternative possible physiological function of diverse neurotransmitter signaling comes from non-mammalian experimental models, such as the lobster and crab, where the neurotransmitters dopamine and 5-HT are capable of axonal action potential initiation, independently of actions at somata and synapses (Ballo et al., 2010; Meyrand et al., 1992; Verdier et al., 2003). Evidence is gathering that modulation of the excitability of axons in mammalian CNS may also have functional implications, e.g. in WM via nicotinic receptors in some pathways (Kawai et al., 2007) and in neonatal rat brain stem WM via GABA-A receptor activation (Kress and Mennerick 2009). It is important to note that this is distinct from classical pre-synaptic effects, where axonal receptors modulate synaptic neurotransmitter release via local action (Trigo et al., 2008).

Summary and Conclusions

It is now clear that neurotransmitter signaling is a prominent feature of myelinated axons in WM and GM, and across a wide range of species including humans. This is notable, because WM is characterised in general by a lack of neurons and synapses, and so neurotransmitter signaling has physiological functions other than neuron-to-neuron communication. A key feature in WM is the apparent predominance of glutamate- and ATP-mediated signaling mechanisms, but this may reflect the physiological techniques we have at our disposal, rather than the true pre-eminence of these neurotransmitters. A common theme is that neurotransmitters evoke Ca^{2+} signals in WM glia, which may be important in the homeostatic functions of astrocytes, whereas in oligodendrocytes they may have specific roles during differentiation and myelination. There is evidence for direct effects of neurotransmitters on axons and this may be important for strengthening conduction of action potentials and maintaining signal integrity along potentially very long projections. Perhaps the most surprising aspect is the diversity of neurotransmitter signaling in WM. Such diversity at GM synapses reflects differences in excitatory, inhibitory and neuromodulatory functions, which is the basis for the phenomenal complexity of neuronal network activity. Why the WM requires so many neurotransmitters is one of the fascinating questions facing those working in the field. A radical hypothesis is that diverse neurotransmitters are capable of axonal action potential initiation and/or modulation of axon excitability. It is possible, therefore, that WM neurotransmitters are involved in some form of information processing.

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