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Cells in focus

Activity-dependent calcium signalling in oligodendrocyte generation

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ABSTRACT

Throughout postnatal life oligodendrocyte progenitor cells proliferate and differentiate into mature myelinating oligodendrocytes in the central nervous system. Neuronal activity is a major external signal controlling this process. Neurotransmitters, or other signalling molecules released in response to neuronal activity, evoke transient increases in intracellular calcium in oligodendrocyte progenitor cells. As calcium can mediate cellular processes, including the transcription of genes involved in oligodendrocyte progenitor cell division and maturation, a rise in intracellular calcium may be a key signal translating changes in neuronal activity into changes in oligodendrocyte progenitor cell behaviour. Here we review recent advances in our understanding of how neuronal activity can evoke calcium signalling in oligodendrocyte progenitor cells.

1. Introduction

Oligodendrocytes progenitor cells (OPCs) are immature cells that can proliferate and differentiate into oligodendrocytes that myelinate axons in the central nervous system (CNS) (Fig. 1). OPCs have highly motile processes (Hughes et al., 2013; Haberlandt et al., 2011) which receive synaptic input from axons (Bergles et al., 2000; Lin and Bergles, 2004). These synapses are retained as OPCs divide but are lost upon differentiation (Kukley et al., 2010). Neuronal activity is one of a number of signals that can influence OPC behaviours such as migration, proliferation, differentiation and myelination (reviewed by Wang and Young, 2014). Herein we evaluate a potential role for calcium signalling in mediating activity-dependent oligodendrocyte generation, as we describe how known products of neuronal activity can or might modulate intracellular calcium levels in OPCs, and examine what is known about how they regulate OPC function.

2. Cell origin and plasticity

2.1. Neuronal activity regulates OPC plasticity

OPCs are generated from neural stem cells during development. They migrate and proliferate to populate the entire CNS where they can generate new myelinating oligodendrocytes throughout life (reviewed by Auderset et al., 2016). Although myelination can occur in the absence of neuronal activity, neuronal activity has been shown to promote OPC proliferation (Li et al., 2010), oligodendrocyte generation (Gibson et al., 2014), the local translation of myelin basic protein (Wake et al., 2011), axon selection (Hines et al., 2015) and the number of myelin internodes produced by each oligodendrocyte (Mensch et al., 2015). While neurons can communicate directly with OPCs *via* specialized synaptic junctions, signalling at these synapses is not needed to bias OPCs to preferentially add new myelin sheathes to electrically active neurons (Wake et al., 2015). Therefore, other methods of communication, such as the spill-over of neurotransmitters from neuron-neuron synapses, non-synaptic release of signalling molecules from axons, or the secondary release of signalling molecules from astrocytes, may be more important for regulating activity-dependent myelin plasticity in the CNS.

3. Functions

For OPC differentiation and subsequent axon myelination to be dependent upon neuronal activity, OPCs must be able to respond appropriately to signals from active neurons. OPCs express an array of receptors and ion channels that allow them to detect products released by active neurons. For example, OPC express receptors for glutamate (Bergles et al., 2000), GABA (Lin and Bergles, 2004) and ATP (Hamilton et al., 2010), which are neurotransmitters that can regulate OPC behaviour (Agresti et al., 2005; Gautier et al., 2015; Zonouzi et al., 2015). As action potential firing can evoke calcium transients in OPCs (Haberlandt et al., 2011; Hamilton et al., 2010; Stevens et al., 2002), this second messenger may determine how

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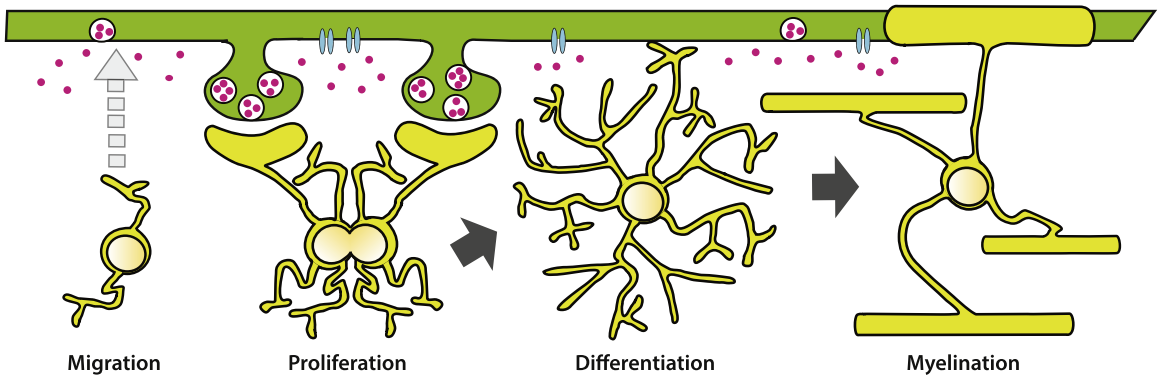

Fig. 1. OPC behaviours regulated by neuronal activity. Neuronal activity can influence the migration, proliferation and differentiation of OPCs, including myelination. However, the intracellular signalling pathways controlling the activity-dependent modulation of these events are poorly understood.

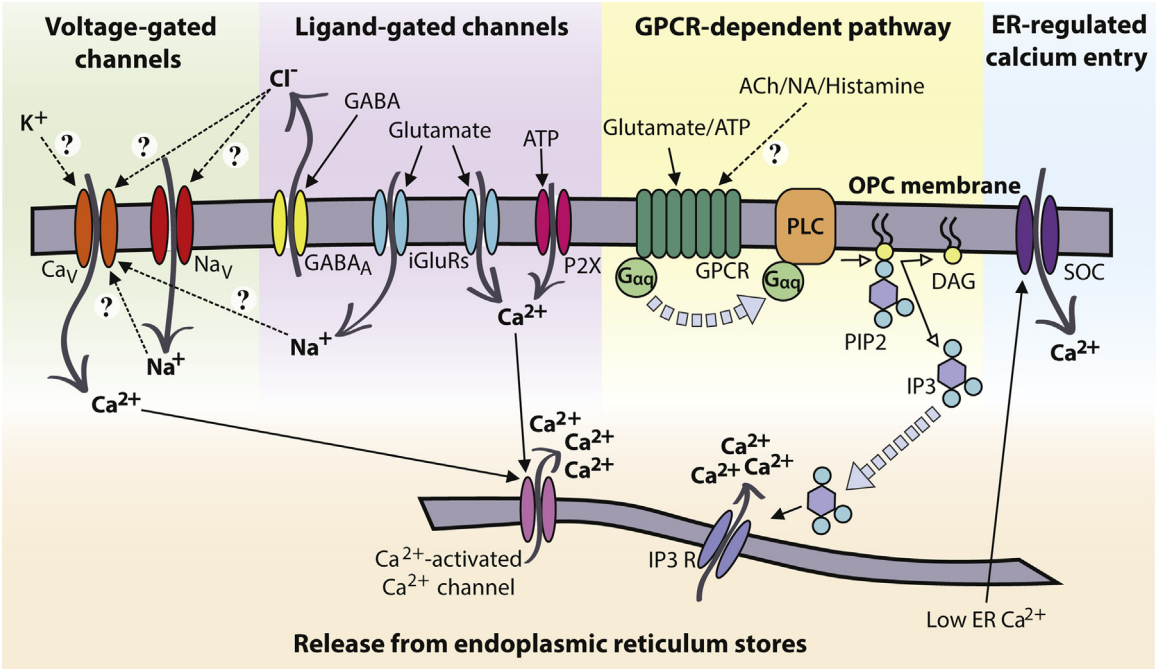

Fig. 2. Multiple pathways can lead to an activity-dependent increase in intracellular calcium in OPCs. Neurotransmitters that have been shown to increase intracellular calcium in OPCs include GABA, glutamate and adenosine triphosphate (ATP). Other products of neuronal activity such as potassium, acetylcholine (ACh), noradrenaline (NA) or histamine may also be able to influence OPC calcium signalling by a variety of mechanisms. OPCs could experience an increase in cytosolic calcium due to the activation of: voltage-gated channels (green); ligand-gated channels (purple); $G\alpha_q$-coupled G-protein coupled receptors (GPCRs) (yellow); calcium channels gated by endoplasmic reticulum (ER) calcium stores (blue), or calcium channels located on the ER (orange). Dark grey arrows indicate direction of ion flux through channels. Thick light grey arrows indicate protein movement. Thin black arrows indicate the activation of ion channels or GPCRs – the solid arrows indicate known actions and the dotted arrows with question marks indicate putative actions in OPCs. Ca_V = voltage gated calcium channel; Na_V = voltage gated sodium channel; $GABA_A$ = γ-aminobutyric acid A receptor; iGluRs = ionotropic glutamate receptors; SOC = store operated channel; IP3 R = inositol 1,4,5-trisphosphate receptor; P2X = P2X purinergic receptor; PLC = phospholipase C; DAG = diacylglycerol; PIP2 = phosphatidylinositol 4,5-bisphosphate.

OPCs respond to signals from active neurons. Here we explore known and potential ways by which products of neuronal activity can elevate intracellular calcium in OPCs (Fig. 2).

3.1. Membrane depolarisation mediates activity-dependent calcium entry in OPCs

Voltage-gated calcium channels (VGCCs) are calcium-permeable ion channels that open in response to membrane depolarisation. They are highly expressed by OPCs but their expression is rapidly downregulated as OPCs differentiate into oligodendrocytes (Cahoy et al., 2008; Larson et al., 2015; Zhang et al., 2014). The major VGCC in OPCs is $Ca_V1.2$ (Cheli et al., 2015). OPC calcium transients induced by neuronal stimulation, involve the activation of VGCCs (Haberlandt et al., 2011). The manner in which neuronal activity could depolarise OPCs to activate VGCCs is unknown, however, it may be the result of neurotransmitter signalling, as γ-aminobutyric acid (GABA) and glutamate can depolarise OPCs by acting at $GABA_A$ chloride channels or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, respectively (Haberlandt et al., 2011; Hamilton et al., 2010). Alternatively, neuronal activity can result in increased extracellular potassium which can depolarise OPCs (Maldonado et al., 2013), and potentially activate VGCCs. VGCC activation may also be