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Invited review

Synaptic retinoic acid signaling and homeostatic synaptic plasticity

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ABSTRACT

One of the defining features of the nervous system is its ability to modify synaptic strength in an experience-dependent manner. Chronic elevation or reduction of network activity activates compensatory mechanisms that modulate synaptic strength in the opposite direction (i.e. reduced network activity leads to increased synaptic strength), a process called homeostatic synaptic plasticity. Among the many mechanisms that mediate homeostatic synaptic plasticity, retinoic acid (RA) has emerged as a novel signaling molecule that is critically involved in homeostatic synaptic plasticity induced by blockade of synaptic activity. In neurons, silencing of synaptic transmission triggers RA synthesis. RA then acts at synapses by a non-genomic mechanism that is independent of its well-known function as a transcriptional regulator, but operates through direct activation of protein translation in neuronal dendrites. Protein synthesis is activated by RA-binding to its receptor RARα, which functions locally in dendrites in a non-canonical manner as an RNA-binding protein that mediate RA's effect on translation. The present review will discuss recent progress in our understanding of the novel role of RA, which led to the identification of RA as a critical synaptic signaling molecule that mediates activity-dependent regulation of protein synthesis in neuronal dendrites.

This article is part of the Special Issue entitled 'Homeostatic Synaptic Plasticity'.

1. Introduction

A dynamic range of network activity is essential for optimal information coding in the nervous system. Normal brain function requires neurons to operate at a constant overall activity level, and to maintain a balance between the relative strength of individual synapses. It is thought that in a neuron, activity levels are kept constant by a process called homeostatic synaptic plasticity (HSP). HSP uniformly adjusts the strengths of a large portion if not all synapses in a neuron to maintain a particular activity level. HSP may be mediated by alterations in pre-synaptic transmitter release, synaptic vesicle loading, postsynaptic receptor function, or neuronal membrane properties (Davis, 2006; Rich and Wenner, 2007; Turrigiano, 2012). Several signaling pathways are involved in various forms of HSP in the mammalian CNS and at the *Drosophila* neuromuscular junction (Turrigiano, 2008; Yu and Goda, 2009). For example, in mammalian neurons, adjustments in the relative expression levels of CaMKIIα vs. IIβ (Thiagarajan et al., 2002) and CaMKIV-regulated transcriptional events (Ibata et al., 2008) mediate homeostatic compensation for changes in neuronal firing and synaptic activity. Additionally, the level of Arc/Arg3.1, an immediate-early gene that is rapidly induced by neuronal activity (Guzowski et al., 2005), modulates homeostatic plasticity through a direct interaction with the endocytic pathway (Shepherd et al., 2006). Recent findings also implicated inactivity-induced postsynaptic synthesis and release of BDNF, which acts retrogradely to enhance presynaptic functions in HSP (Jakawich et al., 2010). At the *Drosophila* neuromuscular junction, homeostatic synaptic plasticity is manifested mainly by changes in presynaptic release modulated by retrograde signaling mechanisms (Davis and Bezprozvanny, 2001), and multiple pathways have been implicated involving molecules such as dysbindin (Dickman and Davis, 2009), Cav2.1 (Frank et al., 2006), the BMP ligand Gbb (Goold and Davis, 2007), Eph receptor and ephexin (Frank et al., 2009), and snapin (Dickman et al., 2012). In addition to these neuronal and muscle-derived molecules, glia-derived factors, such as cytokine TNFα, have been demonstrated to control synaptic strength and to influence HSP (Beattie et al., 2002; Stellwagen and

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Malenka, 2006). Although a bewildering number of different pathways may contribute to HSP, recent progress has identified fundamental events that underlie many forms of HSP in the mammalian nervous system, thereby suggesting that a limited number of basic molecular mechanisms could account for this important process.

Synaptic scaling is a form of HSP that was initially discovered in cultured cortical neurons where neuronal activity was either chronically blocked with tetrodotoxin (TTX), or elevated by inhibition of GABAergic synaptic transmission (Turrigiano et al., 1998). The expression of synaptic scaling is thought to involve transcriptional events that alter the abundance of AMPA-type glutamate receptors in the postsynaptic membrane (Turrigiano, 2012). An important property of synaptic scaling is that all synapses of a neuron are modified concurrently in a multiplicative fashion (i.e. stronger synapses are changed proportionally more than weaker synapses), thereby preserving the relative synaptic weights of the overall circuit (Thiagarajan et al., 2005; Turrigiano et al., 1998) but see Echegoyen et al. (2007). However, several recent studies show that a fast adaptive form of HSP can be induced when excitatory synaptic transmission is blocked in conjunction with TTX treatment (Ju et al., 2004; Sutton et al., 2006, 2004). Importantly, this rapid form of HSP is independent of transcription, and is mediated by the local synthesis and synaptic insertion of homomeric GluA1 receptors, allowing adjustment of synaptic strength at spatially discrete locations in a neuron (Table 1). Although several biochemical signaling pathways can trigger dendritic protein synthesis upon increase in neuronal activity (Kelleher et al., 2004; Klann and Dever, 2004; Schuman et al., 2006), the signaling pathways involved in this type of inactivity-induced synaptic scaling remain largely unclear.

Several years ago we identified retinoic acid (RA) as a key mediator of transcription-independent HSP (Aoto et al., 2008). Here, we will review recent progress in our understanding of the non-canonical role of RA that emerged from this observation, leading to the identification of RA as a novel synaptic signaling molecule that mediates activity-dependent regulation of protein synthesis in neuronal dendrites. We will discuss the function of RA not only in the context of HSP, but also in other forms of synaptic plasticity, and relate the RA-dependent synaptic signaling pathway to neurological diseases. Since this type of RA signaling has only been examined in vertebrates, we will limit our discussion to the vertebrate nervous system.

Table 1
Comparison of mechanistic distinction between RA-dependent and RA-independent homeostatic synaptic plasticity.

RA-dependent homeostatic synaptic plasticity	RA-independent homeostatic synaptic plasticity
Requires blockade of synaptic activity and reduction of dendritic calcium levels (i.e. TTX + APV, CNQX, nifedipine)	Requires action potential blockade only (i.e. TTX), sensitive to somatic calcium levels
Requires local protein translation	Requires transcription events
Involve all synapses or a subset of synapses of a neuron (can be both global and local)	Involves all synapses of a neuron (global)
Requires normal FMRP function	Operates normally in FMRP knockout neuron
Inserts GluA2-lacking calcium-permeable AMPA receptors	Inserts GluA2-containing calcium-impermeable AMPA receptors
Rapid onset and expression	Slower in expression, lags behind the RA-dependent phase of HSP

2. Retinoid signaling in the adult nervous system

Biological sources of retinoids include preformed Vitamin A from animal-derived food, or pro-Vitamin A carotenoids (e.g. β-carotene) from plant-derived foods. The majority of preformed Vitamin A and pro-Vitamin A are converted into all-trans-retinol by a series of reactions in the intestinal lumen and mucosa. Upon absorption into enterocytes, re-esterified retinol is transported to the liver, which is the major site for retinoid storage in the body. Retinol is secreted from the liver in response to the body's needs and is transported in the blood bound to retinol binding protein (RBP). In target cells, a membrane receptor for RBP mediates cellular uptake of retinol (Kawaguchi et al., 2007). Retinol is locally metabolized into its bioactive derivative all-trans-retinoic acid (RA), which exerts its effects in a variety of biological systems.

RA is synthesized from retinol in two oxidation reactions. First, cytosolic retinol dehydrogenase (ROLDH) or alcohol dehydrogenase (ADH) convert retinol to retinal (retinaldehyde). Second, retinal dehydrogenase (RALDH) oxidizes retinal to RA. These enzymes are expressed in the adult mammalian brain (Krezel et al., 1999; Zetterstrom et al., 1999). Local RA synthesis in adult brain has been demonstrated using transgenic mice expressing LacZ downstream of three canonical retinoic acid response elements (RAREs) (Thompson Haskell et al., 2002). Strikingly, in the forebrain, cerebellum and meninges, the rates of RA synthesis are comparable to, or exceed, the rates of RA synthesis in liver (Dev et al., 1993). Taken together, these studies unequivocally establish that RA synthesis occurs in the adult brain (Dev et al., 1993; Wagner et al., 2002). While most studies on RA actions are traditionally focused on its role as a transcriptional activator, various observations mostly in culture systems have demonstrated rapid transcription-independent, non-genomic RA effects that occur at the cellular periphery or at the plasma membrane (Ko et al., 2007; Masia et al., 2007; Uruno et al., 2005). Below we will discuss our recent observations on non-genomic RA actions in brain function: surprisingly, RA exerts a critical control over synaptic strength in HSP, an effect that is rapid and independent of transcription.

During development of the nervous system, spatial RA gradients emanating from localized foci of RA synthesis contribute to brain patterning, morphogenetic effects that are due to the opposing actions of the two main classes of RA metabolic enzymes, the RA-synthesizing RALDHs and the RA-degrading CYP26 enzymes of a cytochrome P450 family (Berggren et al., 1999; Fujii et al., 1997; McCaffery and Drager, 1993; Niederreither et al., 1997; Pennimpede et al., 2010; Ross and Zolfaghari, 2011). Similarly, in mature CNS, RA is not uniformly available but is only present in discrete regions of the brain (Bremner and McCaffery, 2008; Lane and Bailey, 2005). In cultured hippocampal neurons, RA is not detectable when neurons are active (Aoto et al., 2008). RA synthesis is strongly induced by loss of synaptic activity and a decrease in dendritic calcium levels (Wang et al., 2011), supporting its role as an important signaling molecule that modulates neuronal function in an active manner.

The action of RA is primarily mediated by nuclear retinoid receptor proteins called retinoic acid receptors (RAR-α, -β, -γ) and retinoid 'X' receptors (RXR-α, -β, -γ). Like other members of the steroid receptor family, RARs and RXRs are transcription factors. Although structurally similar, the ligand specificity differs between them in that RARs bind all-trans-RA and 9-cis-RA with high affinity, whereas RXRs bind exclusively 9-cis-RA (Soprano et al., 2004). Because 9-cis-RA is undetectable *in vivo*, the effects of retinoids on gene transcription are presumed to be mediated by RA binding to RARs. In the adult mammalian brain, RARα is abundant in the cortex and hippocampus, RARβ is highly expressed in the basal ganglia, and RARγ is not detectable (Krezel et al., 1999; Zetterstrom et al., 1999). Although RARs are concentrated in cell nuclei, they