Journal of Physiology - Paris xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Physiology - Paris

journal homepage: www.elsevier.com/locate/jphysparis

Review Paper

Nicotinic regulation of experience-dependent plasticity in visual cortex

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ARTICLE INFO

Article history:
Received 10 July 2016
Received in revised form 19 September 2016
Accepted 9 November 2016
Available online xxxx

Keywords:
Visual cortex
Plasticity
Cholinergic
Nicotinic
Lynx1
Lypd6

ABSTRACT

While the cholinergic neuromodulatory system and muscarinic acetylcholine receptors (AChRs) have been appreciated as permissive factors for developmental critical period plasticity in visual cortex, it was unknown why plasticity becomes limited after the critical period even in the presence of massive cholinergic projections to visual cortex. In this review we highlighted the recent progresses that started to shed light on the role of the nicotinic cholinergic neuromodulatory signaling on limiting juvenile form of plasticity in the adult brain. We introduce the Lynx family of proteins and Lynx1 as its representative, as endogenous proteins structurally similar to α-bungarotoxin with the ability to bind and modulate nAChRs to effectively regulate functional and structural plasticity. Remarkably, Lynx family members are expressed in distinct subpopulations of GABAergic interneurons, placing them in unique positions to potentially regulate the convergence of GABAergic and nicotinic neuromodulatory systems to regulate plasticity. Continuing studies of the potentially differential roles of Lynx family of proteins may further our understanding of the fundamentals of molecular and cell type-specific mechanisms of plasticity that we may be able to harness through nicotinic cholinergic signaling.

Contents

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http://dx.doi.org/10.1016/j.jphysparis.2016.11.003
0928-4257/

1. Introduction

Early postnatal life is marked by a period of heightened sensitivity to experience that in turn profoundly influences the sculpting of neural circuits. This temporal window when experience provides information to carry development beyond the reaches of early gene programs is known as "critical period", and is the common moment in postnatal life across brain functions when they are potently and rapidly shaped to allow efficient acquisition of adaptive skills and behaviors (Hensch, 2004; Knudsen, 2004). One of the models most used to understand the fundamental mechanisms of critical period plasticity has been the ocular dominance (OD) plasticity of the mammalian primary visual cortex (V1). The obstruction of vision through one eye (monocular deprivation: MD) in early life results an enduring loss of evoked responsiveness of V1 neurons to the deprived eye and an overall decrease in visual function that resembles amblyopia, a visual impairment that endures into adulthood (Wiesel, 1982; Morishita and Hensch, 2008). Now used for over half century, this canonical model has achieved progress particularly in the direction of investigating the regulatory role of the cholinergic neuromodulatory system in critical period plasticity. The end goal of this endeavor is to understand the pathogeneses as well as to develop therapeutic strategies towards neurodevelopmental disorders, where for some of them mutations and deficits in nicotinic cholinergic signaling have been implicated (Klassen et al., 2011; Lin et al., 2014; Yang et al., 2015).

In the present review we discuss the contribution of cholinergic neuromodulatory system, with an emphasis on nicotinic acetylcholine receptors (nAChRs), on experience-dependent V1 plasticity before, during, and after the critical period. We particularly focus on recent discoveries regarding molecular mechanisms that fine-tune the complex cholinergic system to suppress its postnatal developmental role and allow switching its track to the adult role. We introduce the Ly-6/neurotoxin gene superfamily (Lynx family) of proteins and Lynx1 as its representative, as novel modulators of nicotinic cholinergic signaling that effectively regulate the expression of plasticity. Finally, we discuss current research that predicts the plasticity-permitting mechanisms of other members of the Lynx family of proteins.

2. Postnatal development of visual cortex cholinergic neuromodulatory signaling and its role in ocular dominance plasticity during the critical period

2.1. Developmental changes in cortical cholinergic neuromodulatory signaling before the opening of critical period

In the rat cortex, cortical innervations of cholinergic neurons from the basal forebrain sharply arise from birth and reach all cortical layers shortly after the first postnatal week. This was previously measured by observing the change in choline acetyltransferace (ChAT), a marker of cholinergic axon terminals. Nicotinic binding affinity in cortical areas including the V1 also rapidly increase starting the first postnatal week, but then peak after the second week before moderately declining to reach adulthood levels by the end of the third week (Kumar and Schliebs, 1992; Zhang et al., 1998; Tribollet et al., 2004; Doura et al., 2008). Cortical expression of nicotinic acetylcholine receptors (nAChR), including the most common heteromeric α4β2 and the homomeric α7 nAChRs, are also known to undergo rapid increases during early postnatal development (Fuchs, 1989; Kumar and Schliebs, 1992; Bina et al., 1995; Broide et al., 1995, 1996; Cimino et al., 1995). Previous work in the V1 of P12 mice have found that transiently enhanced nicotinic transmission through β2 and α7 nAChRs of the layer VI are necessary for deep layer spine formation and glutamatergic synapse maturation respectively and independently of one another. (Metherate and Hsieh, 2003; Kassam et al., 2008; Kawai et al., 2011; Lozada et al., 2012a, 2012b). Thus establishment of cortical nicotinic cholinergic signaling begins early during the first postnatal weeks for rapid establishment and maturation of cortical glutamatergic connections. However, whether this early developmental pattern and function of nicotinic cholinergic signaling universally applies to all the other cortical regions remains unknown. Further rigorous studies are required to characterize the temporal and spatial patterns of early postnatal development of nicotinic signaling across receptor subtypes and cortical regions and understand their functional roles.

2.2. Cholinergic regulation of ocular dominance plasticity during the developmental critical period

In cortical areas including the V1, nicotinic cholinergic signaling aids the initial postnatal brain development but may continue to further be involved in aiding experience-dependent circuit maturation. Although cholinergic innervation of rat somatosensory and motor cortices peak into adult-like patterns soon after the end of the second postnatal week, the development of V1 and frontal cortex innervation continue to reach adulthood-like levels instead around P32. (Parnavelas et al., 1986; Siciliano et al., 1997; Mechawar and Descarries, 2001; Mechawar et al., 2002) (Fig. 1). While the functional relevance of extended development in these areas are not exactly known, a secondary developmental role for cholinergic signaling may be suggestible. For instance in the V1, the timespan between second postnatal week until P32 evenly coincides with the beginning of visual experience to the rise and decline of the V1 critical period. A classical study featuring pharmacological- and lesion-based manipulations in kittens revealed that cholinergic transmission is indeed necessary for OD plasticity of the V1 (Bear and Singer, 1986). Then later study demonstrated that intracortical infusions of muscarinic antagonists interfere with OD plasticity, and implicated the permissive action of at least the muscarinic component of cholinergic system in OD plasticity during the critical period (Gu and Singer, 1993). In the same study however, pharmacological suppression of nicotinic cholinergic signaling did not block OD plasticity. Still some evidences, albeit correlative, hint a role potentially worth future investigations of nicotinic cholinergic signaling in regulating

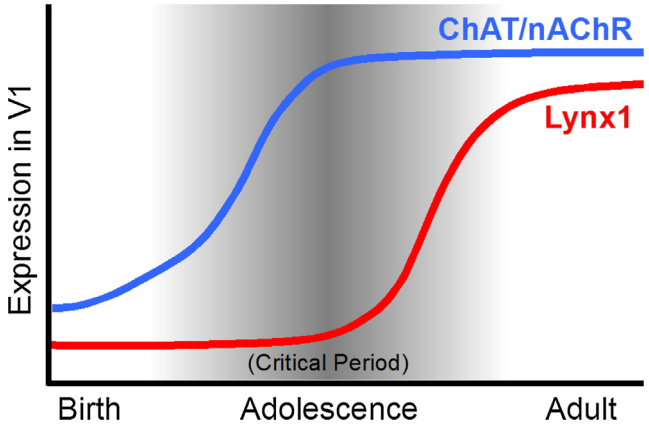

Fig. 1. The expression timecourse of cholinergic innervation, nicotinic acetylcholinergic receptors, and Lynx1 in the primary visual cortex. Cholinergic innervations of the V1 (denoted as ChAT expression) and expression of nAChRs, sharply elevate from birth and continue to follow along the rise of critical period after eye opening. In adulthood, while cholinergic signaling remains robust, Lynx1 increases to actively dampen nicotinic cholinergic signaling to effectively suppress plasticity.

Please cite this article in press as: Sadahiro, M., et al. Nicotinic regulation of experience-dependent plasticity in visual cortex. J. Physiol. (2016), http://dx.doi.org/10.1016/j.jphysparis.2016.11.003