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Nicotinic Regulation of Experience-Dependent Plasticity in Visual Cortex

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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.

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

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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 in 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 pathogenesis 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 acetyltransferase (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 $\alpha 4\beta 2$ and the homomeric $\alpha 7$ 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 $\beta 2$ and $\alpha 7$ 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) (Figure 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 critical period plasticity alongside muscarinic cholinergic signaling. The expression patterns of both $\alpha 7$ and $\alpha 4\beta 2$ nAChRs in the V1 follow time courses that are very similar to that of the development of cholinergic innervations of the V1. Moreover, the expression of $\alpha 7$ is also dependent on visual experience (Siciliano et al., 1997; Mechawar and Descarries, 2001; Aztiria et al., 2004). Yet the precise mechanistic evidence connecting nicotinic cholinergic signaling to regulation of critical period plasticity is hardly confirmed. Therefore future studies will be required to investigate to what extent cortical nicotinic cholinergic signaling causally contributes to critical period plasticity, and if true, through which nAChR subtypes, associated molecules, cortical cell types, and circuits. Interestingly, parvalbumin-expressing (PV) interneurons, implicated in triggering experience-dependent plasticity during the critical period (Kuhlman et al., 2013), are reported to have some direct and indirect associations with $\alpha 7$ nAChRs signaling. Specifically, genetic ablation of *chrna 7* have been shown to exhibit reduced immunoreactivity for PV without impacting the number of PV cells (Lin et al., 2014). However, there are mixed reports on whether or not cortical PV

interneurons themselves express $\alpha 7$ nAChR. While some studies reported the lack of direct nicotinic response (Gulledge et al., 2007) (Arroyo et al., 2014), or lack of $\alpha 7$ nAChR expression in fast-spiking PV interneurons (Couey et al., 2007) (Porter et al., 1999), other studies revealed the expression of $\alpha 7$ nAChR proteins in PV interneurons (Murakami et al., 2013), and demonstrated that cholinergic responses of half of fast-spiking putative PV interneurons in mouse prefrontal cortex was abolished by the addition of the $\alpha 7$ -specific antagonist methyllycaconitine (MLA) but not the non- $\alpha 7$ -specific antagonist Dihydro- β -erythroidine hydrobromide (Dh β E) (Poorthuis et al., 2013). Given the recently recognized heterogeneity of PV interneurons (Tasic et al., 2016), it would be of great interest in future studies to rigorously dissect the potential contribution of $\alpha 7$ nAChR-based signaling in PV interneurons, across various cortical layers and species, to fulfill rapid experience-dependent modulation of PV interneurons required to trigger global plasticity (Kuhlman et al., 2013). In contrast to the dearth of knowledge regarding the role of nicotinic cholinergic signaling during the critical period, there are more evidences regarding the contribution of nicotinic cholinergic signaling in regulating plasticity in adulthood. In the following chapter, we discuss the recent advances that have found that the closure of the V1 critical period into adulthood does in fact directly involve the nicotinic cholinergic neuromodulatory system, and shift focus onto Lynx1 and its family of proteins that can alter nAChR agonist binding and desensitization kinetics (Miwa et al., 1999; Morishita et al., 2010).

3. Regulation of critical period closure by Lynx1, an endogenous brake for nAChRs

While visual cortical nicotinic binding moderately declines into adulthood (Kumar and Schliebs, 1992; Zhang et al., 1998), the massive basal forebrain cholinergic innervation and relative expression of nAChRs, namely of the $\alpha 4$ and $\alpha 7$ subtypes, persists (Mechawar and Descarries, 2001; Aztiria et al., 2004) (Figure 1). If nicotinic cholinergic signaling could regulate critical period plasticity, then how would then plasticity become severely restricted in adulthood even in the remaining presence of robust basal forebrain cholinergic innervation? Here we introduce Lynx1, an allosteric cholinergic modulator that increases into adulthood after critical period, and review its contribution to regulate functional and structural plasticity in the V1 (Bukhari et al., 2015; Morishita et al., 2010; Sajo et al., 2016). The discovery of the role of nicotinic cholinergic modulator Lynx1 as a plasticity regulator has given light to a new perspective – the brain is intrinsically plastic even in adulthood, but is actively masked by molecular plasticity “brakes” (Bavelier et al., 2010).

3.1 Lynx1, an endogenous brake for nAChRs

Lynx1 is a member of the Ly-6/neurotoxin gene superfamily (Lynx family) of proteins that feature a three-looped toxin fold, a structural characteristic shared with the snake venom toxin α -bungarotoxin. Thus as an endogenous prototoxin, Lynx1 can bind directly to the extracellular face of nAChRs (Miwa et al., 1999). Initial analysis of the functional consequence of genetic ablation of Lynx1 in mice revealed that Lynx1 is an allosteric modulator to both the heteromeric $\alpha 4\beta 2$ or the homomeric $\alpha 7$ nAChRs that affects their kinetics, decreases their agonist affinities, and increases their desensitization to overall limit their activation. In effect Lynx1 regulates the efficacies of synaptic sites of nAChR action,

and as one function can serve as a protective measure against neurotoxicity through agonist-induced overstimulation. In fact, genetic deletion of Lynx1 eventually leads to neurodegeneration in aged mice (Miwa et al., 2006). However, it is not known whether the expression of Lynx1 itself is regulated by activity.

3.2 Role of Lynx1 on limiting functional plasticity

The novel role of Lynx1 as a functional brake of cortical plasticity first gained light through a transcriptome analysis in search of molecules in the binocular zone of mouse V1 that are increased in adulthood compared to during the critical period. Lynx1 expression increases both at the mRNA and protein levels in V1, in concert with the closure of the critical period for OD plasticity (Plessy et al., 2008; Morishita et al., 2010) (Figure 1). Intriguingly, the increase of Lynx1 into adulthood was found to actively suppress functional plasticity by acting upon nAChRs. Assessment of OD plasticity in Lynx1 knockout (KO) mice found that removal of Lynx1 prolongs heightened V1 plasticity into adulthood but not without the possibility of “re-masking” the plasticity through active pharmacological blockade of nAChR signaling. In the follow up study, it was further examined to what extent elevated OD plasticity in adult Lynx1 KO mice reflects juvenile forms of plasticity (Bukhari et al., 2015). In juvenile mice, the OD shift after 4 days of MD is mediated primarily by a decrease of deprived contralateral eye response in the V1 (Sato and Stryker, 2008). Bukhari et al. demonstrated that when the normalized visual stimulus evoked firing rates of V1 neurons were compared between MD and no MD groups, the deprived contralateral eye response of adult Lynx1 KO mice after MD is significantly decreased and the non-deprived ipsilateral eye response is just modestly increased, suggesting that removal of Lynx1 unmasks juvenile-like characteristic of experience-dependent plasticity (Bukhari et al., 2015). In addition, adult Lynx1 KO mice that underwent long-term MD during the V1 critical period to artificially induce visual functional impairment modeling amblyopia showed spontaneous recovery of visual acuity to normal levels simply when the visually deprived eye was reopened (Morishita et al., 2010). Thus the allosteric inhibition of nAChR signaling by Lynx1 in adulthood masks cortical plasticity even in the continual persistence of massive cholinergic innervation from the basal forebrain. Consequently, the removal of Lynx1 results in a restoration of nAChR function to adolescent level as well as subsequent resurgence of experience-dependent plasticity.

3.3 Role of Lynx1 on limiting structural plasticity

Structural plasticity is likely prerequisite to the progression of functional plasticity that is inducible during the critical period as well as in the state where functional brakes are removed. During the juvenile critical period, short term MD produces not only robust functional OD plasticity measured electrophysiologically (Fagiolini et al., 1994; Gordon and Stryker, 1996), but also structural plasticity, the elevated motility and reduction of dendritic spines (Mataga et al., 2004; Oray et al., 2004). Importantly, such juvenile form of structural plasticity becomes limited in the adult V1. Recent study showed that in the V1 of adult Lynx1 KO mice there is a significant MD-dependent density reduction of the stubby spines and thin spines (but not mushroom spine) of distal apical dendritic spines of the V1 neurons in layer II/III following MD in comparison to its WT counterparts (Bukhari et al., 2015). These results are consistent with previously published results demonstrating the correlation

of stubby spine (Christoffel et al., 2011; Golden et al., 2013) and thin spine (Dumitriu et al., 2010) subtypes and brain plasticity. The observed structural plasticity is also consistent with a MD-dependent decrease in the response of the deprived contralateral eye in the V1, a signature of juvenile-like plasticity (Bukhari et al., 2015).

Importantly, spine turnover is also known to decline into adulthood (Grutzendler et al., 2002; Holtmaat et al., 2005). Through the use of *in vivo* chronic imaging using two-photon microscopy, Sajo et al. recently examined the contribution of Lynx1 on dendritic spine turnover before and after MD in the adult V1 by measuring the spine turnover rate of apical dendrites of layer 5 and 2/3 pyramidal neurons in adult Lynx1 KO mice (Sajo et al., 2016). They found that the deletion of Lynx1 doubled the baseline spine turnover rate, suggesting that the spine dynamics in the adult cortex is actively limited by the presence of Lynx1.

Sajo et al. also demonstrated that after MD, while spine gain rate of layer 5 neurons becomes comparable between adult Lynx1KO mice and adult WT mice due to MD-induced increase in spine gain in WT mice (Hofer et al., 2009), spine loss rate remains significantly higher in Lynx1KO mice compared to WT matched controls in both layer 5 and 2/3 neurons (Sajo et al., 2016). These results suggested that, while spine gain rate correlates well with the residual plasticity in the normal adult V1, higher spine loss seems to be a good correlate of elevated juvenile-like functional plasticity in adult Lynx1KO mice. Interestingly, in adult Lynx1KO neurons, MD induced a reduction in spine loss rate, with no change in gain rate (Sajo et al., 2016), in contrast to adult wild type L5 neurons, where it is known that MD increases their spine gain rate with no change in loss rate (Hofer et al., 2009). Given that juvenile mouse barrel cortex also similarly exhibits whisker-trimming-induced reduction of spine loss (Zuo et al., 2005), the experience-dependent changes observed in Lynx1KO mice reflect characteristics of the juvenile but not adult WT brain. In order to fully understand how the altered spine dynamics in Lynx1KO mice can contribute to the elevated functional OD plasticity in adult Lynx1-KO mice, it is necessary to know the ocular dominance of each spine formed or lost during MD. The use of current advanced calcium imaging technique that allows visualization of neuronal activity at the single-spine level through the use of recently developed genetically encoded fluorescent sensors (GCAMP6) will allow future studies to address this question (Chen et al., 2013).

3.4 Mechanism of Lynx1 based regulation of functional and structural plasticity

Collectively the findings regarding Lynx1 suggests a direct relationship between plasticity regulation and nicotinic signaling, and underlines the significance of fine tuning of nicotinic tone to vastly control the development of brain functions. The details of the plasticity mechanisms that are masked by Lynx1 in adulthood are only partially known. However recent progress suggests that both the functional and structural aspects of plasticity limited by Lynx1 in the adult brain involve the regulation of proteolytic signaling system previously identified to be required for juvenile-like plasticity. Bukhari et al. recently demonstrated that removal of Lynx1 unmasks experience-dependent increase of extracellular proteolytic activity, specifically of tissue plasminogen activator (tPA), a major serine protease in the brain (Bukhari et al., 2015). Previous studies showed that during the critical period (but not in adulthood), MD rapidly leads to upregulation of tPA followed by rapid pruning of spines

along the apical dendrites of V1 pyramidal neurons. Consequently, ablation of tPA results in an impairment of juvenile OD plasticity (Mataga et al., 2002, 2004; Oray et al., 2004). Consistent with the role of tPA in regulating both functional and structural plasticity, Bukhari et al. further demonstrated that both structural and functional plasticity in adult Lynx1KO mice are dependent on tPA activity, as simultaneous ablation of tPA prevents the MD-dependent loss of spines and OD plasticity. Thus removal of Lynx1 leaves tPA activation unfettered, allowing experience-dependent elevation of proteolysis that facilitates dendritic spine reduction, which in turn mediates functional plasticity (Bukhari et al., 2015). Elucidating how Lynx1 limits experience-dependent tPA activation will be an important area of future exploration. tPA activation may be an indirect downstream event that is part of the mechanism mediating plasticity and is commonly regulated by many negative regulators of plasticity, such as chondroitin sulfate proteoglycans (CSPGs), the myelin inhibitor protein, Nogo66 receptor 1 (NgR1), Paired-immunoglobulin-like receptor B (PirB), and Cartilage link protein (Crtl1). Alternatively, as tPA expression itself is known to be regulated by neural activity (Qian et al., 1993), elevated tPA activity in Lynx1KO mice may be a consequence of altered network activity in local excitatory and inhibitory neural network in V1 (Caroni et al., 2012), as predicted from an observation that an enhanced inhibition in V1 by diazepam treatment abolishes the OD plasticity in adult Lynx1KO mice (Morishita et al., 2010). In future studies, cell-type specific manipulation of Lynx1 expression in combination with *in vivo* recording/imaging of excitatory and inhibitory synapses will allow dissection of the role of Lynx1 in modulating activity at the network level. In addition, further studies are also necessary to study whether Lynx1 expression *per se* is regulated in activity/experience-dependent manner at both transcriptional level and post-translational level (e.g. shedding of GPI anchor).

Determination of the targets of activated tPA in the Lynx1-based plasticity pathway will be important in future studies. Mataga and colleagues previously discussed BDNF, NCAM, laminin, and CSPGs as potential molecular and structural targets of tPA in the juvenile brain (Mataga et al., 2002, 2004; Oray et al., 2004). Unlike the juvenile brain, the extracellular matrix of the adult brain is rich in CSPGs (Pizzorusso et al., 2002; Cabungcal et al., 2013; de Vivo et al., 2013). Interestingly, Bukhari et al showed that tPA can degrade CSPGs and allow for enhanced recovery in adult CNS injury models (Bukhari et al., 2011). Whether related or distinct mechanisms are involved in Lynx1-based plasticity regulation is an important future question.

4. Lynx family of proteins: A potentially diverse array of nicotinic plasticity regulators

Within the vast Lynx family of proteins, a handful of its members other than Lynx1 are enriched in the mammalian CNS, and those also may potentially serve similar yet distinct roles in regulating plasticity (Miwa et al., 2012a). For instance, Lynx2, a closely related fellow Lynx family member, declines as the critical period closes and is expressed in the V1 almost entirely in excitatory cells (Morishita et al., 2010; Demars and Morishita, 2014). Indeed other than regulation of plasticity in the V1 by Lynx1, other Lynx family members have also been associated with learning and memory functions, sensorimotor gating, and

anxiety related behaviors. However little is known of whether they also contribute to the regulation of plasticity (Miwa et al., 2006, 2012b; Darvas et al., 2009; Tekinay et al., 2009). Potentially Lynx family members may differentially modulate nAChRs, across different cell types and receptor subtypes to differentially regulate plasticity. Ultimately, 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.

4.1 Differential modulatory mechanism and expression of Lynx family members across GABAergic interneuron subtypes

Most of the members of the Lynx family including Lynx1 are thought to inhibit signaling through nAChRs. However, at least one member called Lypd6 is known to potentiate calcium currents through nAChRs in direct contrast to the action of Lynx1 (Darvas et al., 2009). Nicotine induced calcium currents in trigeminal ganglion neurons in Lypd6 overexpressing mice were blocked by the broad spectrum nAChR antagonist mecamylamine, but were unaffected by the nAChR α 7 selective inhibitor, α -bungarotoxin (α -Btx) and MLA (Darvas et al., 2009), indicating the specific involvement of non- α 7-nAChRs (in other words $\alpha\beta$ - heteromers of nAChRs) in these responses. Moreover, in our unpublished observation we found that while Lynx1 expression elevates into adulthood, on the other hand the expression of Lypd6 declines. As Lynx1 inhibits but Lypd6 potentiates nAChR signaling, these expression patterns collectively suppress nAChR signaling in adult V1 (Sadahiro et al unpublished observation) (Figure 2A). Differential modulation of nAChR signaling by Lynx1 and Lypd6 across receptor subtypes and even cell types may suggest versatile ways of modulating of nicotinic tone in order to regulate plasticity. A recent study by Demars and Morishita revealed that both Lynx1 and Lypd6 were preferably enriched in GABAergic interneurons than glutamatergic neurons in the V1, while other Lynx family members such as Lynx2 and Lypd6b are more enriched in glutamatergic neurons than in GABAergic interneurons in V1 (Demars and Morishita, 2014). Furthermore within the GABAergic interneuronal subpopulations, Lynx1 and Lypd6 expression distinctly preferred PV and somatostatin-expressing (SST) interneurons respectively (Demars and Morishita, 2014) (Figure 2B).

Lynx1 has been shown to bind to the homomeric α 7 and heteromeric α 4 β 2 containing nAChRs (Ibañez-Tallon et al., 2002). Taking together the association of PV interneurons with both Lynx1 (Demars and Morishita, 2014) and α 7 nAChR (Poorthuis et al., 2013) (Murakami et al., 2013), it can be predicted that the function of Lynx1 in masking cortical plasticity could be mediated at least in part through homomeric α 7 nAChRs specifically in cortical PV interneurons. The somatodendritic domain of PV-interneurons is enwrapped by one of the targets of tPA, the extracellular matrix proteins that comprise the perineuronal nets (PNNs). It is intriguing that the disruption of PNNs can reactivate visual plasticity in adult animals (Pizzorusso et al., 2002). As tPA activity can elevate within 1 day after monocular deprivation (Mataga et al, 2002), PNNs are predicted to be well positioned to be immediately subjected to proteolysis to rapidly modulate perisomatic inputs onto PV-cells and in turn the activity of PV-circuits (Kuhlman et al, 2013). As experience-dependent tPA activity is prevented by Lynx1 (Mataga et al., 2002, 2004; Bukhari et al., 2015), elevated

Lynx1 in adulthood, through its action upon the $\alpha 7$ -containing nAChRs, may actively suppress the capacity of PV interneurons to undergo rapid experience-dependent changes necessary for triggering global plasticity (Kuhlman et al., 2013). Future study is necessary to test this possibility.

4.2 Lypd6 enrichment in SST interneurons: A potential positive modulator of OD plasticity?

The preference of expression in SST interneurons and the positive modulatory effect of Lypd6, which completely departs from characteristics of Lynx1, are of significant interest since the role of SST interneurons in regulating plasticity has hardly ever been addressed until recently (Tang et al., 2014; Fu et al., 2015). Most cortical SST interneurons are Martinotti-type cells, which send their axons into superficial layers and form dense axon collateral networks (McGarry et al., 2010). Interestingly, Lypd6 is specifically expressed in a subpopulation of SST interneurons located in deep cortical layers (layers 5 and 6) of V1 (Demars and Morishita, 2014). Previous studies reported mixed results regarding nicotinic response of cortical SST interneurons. While some studies reported lack of nicotinic response in neocortical SST interneurons (Gulledge et al., 2007) (Arroyo et al., 2014) (Porter et al., 1999), others reported the contrary (Poorthuis et al., 2013) (Chen et al., 2015). It is possible that the minor subpopulation of deep layer SST interneurons that express Lypd6 was not well represented in the previous negative reports. Although the detailed characteristics of this minor cortical subpopulation of SST interneurons is yet to be known, interestingly in the hippocampus there is a morphologically and electrophysiologically similar population of SST interneurons found in the oriens-lacunosum moleculare (O-LM) that have high responsiveness to nicotinic signaling and also happen to express Lypd6 (Heys et al., 2012; Demars and Morishita, 2014). Interestingly, hippocampal O-LM SST interneurons (Jia et al., 2010) are known to express $\alpha 2$ -containing nAChR with a unique non-desensitizing characteristic that allows continual activation and calcium entry in the presence of nicotine, which mediates nicotine-facilitated LTP induction in these neurons (Jia et al., 2010). Lypd6 is perhaps an ideal candidate to mediate or modulate these activities through its ability to directly heighten calcium currents potentially through $\alpha 2$ nAChRs. The $\alpha 2$ nAChR subunit is the most sparsely expressed subunit across the brain, but is notably expressed in the SST interneurons of the V1 layers 5 and 6 where Lypd6 is also expressed (Tasic et al., 2016). Within cortical circuits, little is known about the involvement of SST interneurons in experience-dependent plasticity. However their positioning within cortical circuits make them an intriguing candidate for triggering OD plasticity (Jiang et al., 2015). Thus manipulating the expression of Lypd6 may potentially be key to modulating their activity to enable their impact on plasticity (Figure 2B). SST interneurons highly innervate local PV interneurons, placing them in an ideal position to drive the rapid inhibition instructive to experience-dependent plasticity (Cottam et al., 2013; Hioki et al., 2013; Pfeffer et al., 2013; Jiang et al., 2015). Additionally, SST interneurons may directly mediate plasticity mechanisms through the inhibition of incoming information to the distal dendrites of pyramidal neurons (Silberberg and Markram, 2007). Collectively, these observations highlight the importance of future work designed to elucidate the role of SST interneurons in OD plasticity and how molecular modulators of nicotinic signaling, such as Lypd6, may mediate these actions.

5. Conclusion and Perspective

Although the cholinergic system and muscarinic AChRs have been appreciated as permissive factors for critical period plasticity (Bear and Singer, 1986; Gu, 2003), it was unknown why plasticity becomes limited after the critical period even in the presence of massive cholinergic projections to V1. In this review we highlighted the progress in the last 5 years that started to shed light on the role of the nicotinic cholinergic neuromodulatory system on regulating plasticity in adulthood. It is now established that the endogenous prototoxin Lynx1 expresses into adulthood as a functional “brake” of plasticity, and ultimately limits plasticity to maintain stability of mature cortical networks by tuning nicotinic signaling in the continual presence of cholinergic innervation. We also discussed the potential contribution of other Lynx family members such as Lypd6 on regulating plasticity. However, critical knowledge gaps exist on how the Lynx family regulates plasticity. Specifically, we lack the knowledge of the key mechanisms such as the identities of specific cell-types, nAChR subtypes, and circuits mediating the plasticity regulated by each Lynx family member. We also know little of to what extent nAChRs and Lynx family members contribute to multiple forms of plasticity other than OD plasticity which are known to involve cholinergic signaling (Goard and Dan, 2009; Kang and Vaucher, 2009; Chen et al., 2012; Pinto et al., 2013; Sur et al., 2013; Kang et al., 2014). Ultimately, 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.

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Highlights

- Cholinergic system is permissive for juvenile ocular dominance plasticity
- Nicotinic brake Lynx1 limits juvenile-like functional plasticity in adulthood
- Lynx1 limits dendritic spine dynamics in adult visual cortex
- Lynx family members are expressed in distinct subpopulations of GABA neurons

Figure 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.

Figure 2. The Lynx family of proteins as novel class of nicotinic cholinergic signaling modulators for regulating plasticity

A. Lynx1 and Lypd6 are representatives of the Ly-6/neurotoxin gene superfamily (Lynx family) of proteins and are negative and positive modulators of nAChR signaling respectively. Lynx1 elevates in expression while Lypd6 expression declines into adulthood. These expression patterns collectively dampen nAChR signaling in adult V1, and well positioned to subsequently suppress cortical plasticity. **B.** Lynx1 and Lypd6 are both preferably enriched in GABAergic interneurons than glutamatergic neurons in the V1, and furthermore within the GABAergic interneuronal subpopulations, they distinctly prefer PV and SST interneurons respectively. While future work should aim to investigate the PV interneuron-specific role of Lynx1 in suppressing cortical plasticity in adulthood, it would be of equal interest to investigate the potential involvement of SST interneurons and the associated nAChR subtype in mediating cortical plasticity where the expression of Lypd6 during the critical period could modulate their impact. The cortical circuit positioning of the SST interneurons as well Lypd6 being a positive modulator of nicotinic cholinergic

signaling highlights an ideal position to drive inhibition that can efficiently mediate experience-dependent plasticity mechanisms.

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