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Regulation of synaptic plasticity in hippocampal area CA2

Kelly E. Carstens and Serena M. Dudek*

Neurobiology Laboratory, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, North Carolina 27709, USA

Abstract

Synaptic plasticity in the hippocampus is thought to play a vital role in both the refinement of neuronal circuits during development and in learning in the mature brain. Synapses in hippocampal area CA1 are known for a robust capacity for long-term potentiation (LTP), whereas synapses in the stratum radiatum of hippocampal area CA2 are particularly resistant to such changes. Although we have yet to fully understand the mechanisms behind this resistance to plasticity, a number of genes and extracellular matrix components highly expressed in CA2 appear to function as molecular brakes on plasticity and develop postnatally in the rodent brain. Curiously, the developmental profile of several CA2-enriched molecules is suggestive of a still undefined critical window of plasticity in the hippocampus.

Introduction

Synaptic plasticity is thought to play a critical role in both the activity-dependent refinement of neuronal circuits during development and in learning in the mature brain. Accordingly, the regulation of synaptic plasticity as a function of postnatal development has been the subject of intense study. This is particularly the case in primary sensory areas of the cerebral cortex, where disruption of normal circuit development by sensory manipulation is limited to critical windows of development, which are also known as critical or sensitive periods. In many of these areas, coincident with the down-regulation of functional plasticity with age, is that both long-term potentiation and depression (LTP or LTD, respectively) of excitatory synaptic transmission and synaptic scaling also decrease over the course of postnatal development [1–3]. Although many of the cellular mechanisms underlying this down regulation of glutamatergic synaptic plasticity in the cortex are also seen in the hippocampus (NR2A:2B ratio of expression, for example [4]), the dramatic reduction of LTP in the neocortex does not occur in the hippocampus. NMDAR-dependent LTD in the hippocampus, on the other hand, does show a developmental down-regulation [5], indicating that specific types of plasticity can be differentially regulated. Interestingly, the capacity for robust LTP, even within the hippocampus, differs between regions; LTP can be readily induced in areas CA1 and dentate gyrus (DG), whereas synapses from CA3 in hippocampal area CA2

*Corresponding author: Dudek, Serena M (dudek@niehs.nih.gov).

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stratum radiatum (SR) are uniquely resistant to the induction of LTP using typical protocols [6]. Curiously, this lack of LTP in CA2 is restricted to synapses in SR as LTP can be readily induced at inputs from the entorhinal cortex (EC) in the stratum lacunosum moleculare (SLM) [7].

CA2 pyramidal neurons are morphologically distinct in that their cell somas are typically larger than CA1 cells and their dendrites lack thorny excrescences (postsynaptic specializations associated with mossy fiber synapses) that are characteristic of CA3 pyramidal neurons [8]. Most, but not all pyramidal neurons in mouse CA2 receive input from the dentate gyrus granule cells, including those that are born in adulthood [9,10]. In addition to the direct inputs from CA3 Schaffer collaterals (SC) in the SR, and EC layer II in the SLM, CA2 neurons receive a defining input from the supramammillary nucleus (SuM) [9,11]. Of particular interest are also the inputs from oxytocin- and vasopressin-containing axons from the paraventricular nucleus (PVN) of the hypothalamus, among others [12,13]. In turn, CA2 neurons provide a major input to the stratum oriens (SO) of CA1 [9,14], as well as to a number of extrahippocampal targets including the lateral septum [12]. Most relevant to the topic of this review, though, is that CA2 pyramidal neurons also exhibit unique cellular signaling pathways regulating synaptic plasticity and respond to several neuromodulators in a way not seen elsewhere in the hippocampus.

Plasticity suppression in CA2

A number of proteins and extracellular matrix components highly expressed in CA2 pyramidal neurons appear to function as molecular brakes on plasticity in the SR (Figure 1) [8]. One or more of these mechanisms likely involves regulation of intracellular calcium levels [15]. Synaptic plasticity requires activity-dependent elevations in calcium in the postsynaptic cell, which ultimately trigger calcium-dependent signaling cascades [16]. Evidence that calcium signaling is limited in CA2 dendrites and spines was found by Simons and colleagues using calcium imaging: CA2 pyramidal neurons had smaller rises in free calcium in response to depolarization due to a significantly faster rate of calcium extrusion and greater buffering capacity compared to responses in neighboring CA1 neurons [17]. LTP could ultimately be induced in CA2 at SR synapses by elevating intracellular calcium, either by blocking calcium extrusion in the postsynaptic cell using an inhibitor of plasma membrane calcium ATPases (PMCA) or by elevating extracellular calcium to 10 mM. These data, in addition to the enrichment of several other calcium/calmodulin-associated proteins in CA2 such as Purkinje cell protein 4 (PCP4), strongly suggests that robust calcium handling properties play an important function in limiting synaptic plasticity in CA2 [8].

Another protein highly expressed in CA2 that suppresses LTP is RGS14 (regulator of G-protein signaling 14); mice lacking RGS14 express robust LTP at CA2 SR synapses [18]. RGS14 is thought to act as a scaffolding protein that negatively regulates ERK/MAPK activation and inhibits signal transduction by driving G-protein α subunits into their inactive state [19]. In addition though, recent work has shown that RGS14 also binds several proteins linked to calcium signaling, such as calmodulin and CaMKII, indicating that RGS14 is also likely to be important in regulating calcium signaling pathways in CA2 [20]. Consistent with

these findings, RGS14 appears to regulate spine calcium levels related to structural plasticity [21]. Thus, it is apparent that we are just beginning to understand the mechanisms by which RGS14 regulates synaptic plasticity in CA2.

The specialized extracellular matrix (ECM), perineuronal nets (PNNs), provide yet another brake on plasticity [22,23]. PNNs are predominantly localized around inhibitory neurons throughout the brain and spinal cord, however in CA2, PNNs also surround excitatory pyramidal neurons and their dendrites and spines [22,24]. Several mechanisms by which PNNs could restrict plasticity have been proposed. One idea is that because PNN component chondroitin sulfate proteoglycans (CSPGs) carry a strong negative charge, they may serve as a buffer of calcium or other cations required for the induction or maintenance of plasticity [25,26]. However, Carstens, et al., observed no changes in paired-pulse facilitation upon disruption of PNNs, which may have been expected if PNNs were limiting synaptic calcium entry [22]. Alternatively, PNNs may be regulating AMPA receptor lateral motility [27,28]. Future studies examining how PNNs function to restrict plasticity at CA2 synapses will be critical to understanding the role of PNNs in the context of other regulators of plasticity in CA2. An interesting conundrum remaining though, is that neither PNNs, nor any of the other potential plasticity brakes mentioned above, appear to be excluded from the CA2 dendrites and synapses in the SLM, which apparently support LTP [7]. Thus, an outstanding question is how synapses in the SR differ from those in the SLM with regard to supporting or suppressing plasticity in CA2. A role for presynaptic LTP in CA2 SLM is one possible explanation.

Another form of plasticity seen in CA2 involves a reduction of feedforward inhibition onto CA2 pyramidal neurons [29–31]. Similar to that observed in CA1, inhibitory synapses from parvalbumin-expressing neurons onto CA2 can undergo LTD in response to a high frequency stimulation of CA3 inputs in SR or by pairing stimulation of input from CA3 and EC (input timing-dependent plasticity; ITDP), causing a net enhancement of CA3-CA2 postsynaptic responses. In contrast to that seen in CA1, this inhibitory LTD in CA2 requires delta opioid receptors. The disinhibition of CA2 responses is also observed at cortical inputs from EC in CA2 SLM [30]. Thus the peculiarities of CA2 are not restricted the excitatory synapses and include circuit dynamics with unique pharmacology.

Developmental changes in CA2

One of the most striking and interesting features of CA2 is that many of the genes highly expressed in CA2 do not appear until the second postnatal week in development in mice [22,32], Allen Mouse Brain Atlas (ABA)[33] (Figure 2). For example, RGS14 mRNA and protein increase during postnatal development, with the protein first detected in mouse CA2 at postnatal day 7 (P7) and maximally expressed in adulthood [32]. Similarly, PCP4, the adenosine A1 receptor, and Striatal Enriched Phosphatase (STEP; Ptpn5), all with potential to negatively modulate synaptic plasticity, also increase with age in a way that mirrors that of RGS14 (ABA; [33–36]; Figure 2). Reminiscent of the critical periods described for a number of sensory systems, though, are the PNNs. Notably, their deposition tracks closely the closure of several critical windows of plasticity and functions to dampen synaptic

plasticity [23]. PNNs in CA2 first appear in early postnatal development, around P14 in the mouse, and increase in expression with age [22,37] (Figure 2).

PNN maturation in several sensory brain regions requires normal experience during postnatal development. To test whether PNNs can be similarly modulated by experience in CA2, Carstens, et al., reared mice in an enriched environment. They found that staining for PNNs in CA2 was greater in these animals, compared to those raised in standard caging [22]. Similar to what was observed in visual cortex *in vivo* [38], treatment of P14–18 mouse hippocampal slices with the enzyme chondroitinase (ChABC) enables LTP in CA2 with SR stimulation. This ‘restoration’ of LTP in CA2 with acute ChABC treatment was not due to enhancement of excitability, although changes in cell excitability were observed with ChABC treatment *in vivo* on a longer timeframe [39]. These findings suggest that PNNs in CA2 function as a negative regulator of synaptic plasticity in early postnatal development and that their maturation is dependent on normal early-life experience. Thus, we speculate that this developmental emergence of plasticity-limiting molecules in CA2 is suggestive of a critical developmental period after which normal LTP at CA3-CA2 synapses is strongly suppressed.

In addition to the appearance of plasticity-restricting molecules in neonatal rodents, age-dependent changes in CA2 also occur later in adolescence. In a study of a mouse model of the neuropsychiatric disorder, 22q11.2 deletion syndrome, the density of parvalbumin positive inhibitory neurons was decreased in CA2 at 8 weeks of age, but not at 4 weeks, compared to control animals [40]. The timing of these alterations in adolescence coincides with the onset of symptoms of 22q11.2 deletion syndrome in human early adulthood. These findings are also particularly relevant to a postmortem study of tissue from individuals with schizophrenia, another neuropsychiatric disorder where symptoms develop later in human adolescence, reporting that the number of non-pyramidal neurons is reduced in area CA2 compared with tissue from unaffected individuals [41,42]. Taken together, CA2 network inhibitory tone and pyramidal cell excitability may be susceptible to disruption specifically during adolescent development. Future studies focusing on the development of inhibitory transmission in CA2 are needed to determine whether feedforward inhibition in CA2 may be another regulator of a possible critical window of plasticity in CA2, as evidenced in several cortical sensory regions [43].

Plasticity inducers in CA2

Synaptic plasticity in CA2 is also regulated by several neuropeptides and neuromodulators. Specifically, receptors for the social neuropeptides vasopressin and oxytocin are enriched in rat and mouse CA2 and can enable synaptic potentiation [44, 45]. Importantly, these neuropeptides play a role in modulating social behavior, aggression, and anxiety [44–46]. Bath application of agonists of either receptor is sufficient to induce a significant potentiation at CA2 SR excitatory synapses in hippocampal slices, but not at CA1 synapses at similar concentrations [44]. This form of vasopressin- and oxytocin-induced potentiation is mechanistically similar to LTP in its dependence on NMDA receptors, calcium, and CaMKII. A second peptide hormone, Substance P, likely originating from SuM inputs, is also capable of inducing NMDA-dependent potentiation in CA2 [47]. Although Substance P

is considered to be important in nociceptive processes, SuM inputs to the hippocampus have also been linked to several types of behavior, including arousal [48,49].

CA2 synapses can also be potentiated by caffeine and other antagonists of the adenosine A1 receptor (A1R), which is highly enriched in rat CA2 [35]. Unlike vasopressin-induced potentiation, caffeine-induced potentiation is independent of NMDA receptors and CaMKII, but is blocked by inhibitors of adenylyl cyclase or PKA [50]. Thus modulation of synaptic plasticity in CA2 may be an important regulator of behavior; several recent studies have now implicated CA2 in novelty detection, spatial memory, social recognition memory, and aggression [8]. The social and aggression behaviors are likely linked to the direct innervation of CA2 by vasopressinergic projection neurons in the PVN [51]. Mice deficient in the vasopressin and oxytocin receptors have deficits in social recognition memory and aggression [52] and viral delivery (replacement) of the vasopressin 1b receptor in dorsal CA2 neurons of knockout mice is sufficient to restore normal aggressive behavior [44]. Most recently, Smith and colleagues found that social recognition memory can be strongly enhanced by optogenetic stimulation of vasopressin inputs into CA2 [51]. Hence, although CA2 synapses in SR appear to be resistant to typical protocols of inducing LTP, a number of modulators appear to be capable of enabling or inducing changes.

Conclusions

The data discussed here raise the question as to what the role of early restriction of plasticity in CA2 could be in regulating CA2 behavioral function. For the most part, hippocampal synaptic plasticity, particularly LTP, is maintained throughout adulthood and is thought to underlie formation of several types of memory. Nevertheless, the postnatal development of plasticity-inhibiting molecules in CA2 is strongly suggestive of a possible critical period of early learning. Critical periods related to hippocampal function have been described. For example, adult rodents and humans are generally unable to recall memories of their early life (referred to as infantile amnesia), and the ability to maintain long-term declarative-like memory improves with postnatal age [53]. A leading explanation for infantile amnesia pertains to hippocampal neurogenesis as the developmental decline in hippocampal neurogenesis corresponds with the ability to form stable long-term memories [53]. However, because of the apparent lack of typical plasticity in adult CA2 SR, we speculate that CA2 may also play a key function in regulating a possible critical window of hippocampal plasticity, perhaps related to social memory and/or aggression. Future studies integrating CA2 plasticity regulation and behavior will be integral for the discovery a possible sensitive period in hippocampal development.

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References:

1. Crair MC, Malenka RC: A critical period for long-term potentiation at thalamocortical synapses. *Nature* 1995, 375:325–328. [PubMed: 7753197]

2. Dudek SM, Friedlander MJ: Developmental down-regulation of LTD in cortical layer IV and its independence of modulation by inhibition. *Neuron* 1996, 16:1097–1106. [PubMed: 8663986]
 3. Turrigiano G: Homeostatic synaptic plasticity: local and global mechanisms for stabilizing neuronal function. *Cold Spring Harb Perspect Biol* 2012, 4:a005736. [PubMed: 22086977]
 4. Philpot BD, Cho KK, Bear MF: Obligatory role of NR2A for metaplasticity in visual cortex. *Neuron* 2007, 53:495–502. [PubMed: 17296552]
 5. Dudek SM, Bear MF: Bidirectional long-term modification of synaptic effectiveness in the adult and immature hippocampus. *J Neurosci* 1993, 13:2910–2918. [PubMed: 8331379]
 6. Zhao M, Choi YS, Obrietan K, Dudek SM: Synaptic plasticity (and the lack thereof) in hippocampal CA2 neurons. *J Neurosci* 2007, 27:12025–12032. [PubMed: 17978044]
 7. Chevalleyre V, Siegelbaum SA: Strong CA2 pyramidal neuron synapses define a powerful disinaptic cortico-hippocampal loop. *Neuron* 2010, 66:560–572. [PubMed: 20510860]
 8. Dudek SM, Alexander GM, Farris S: Rediscovering area CA2: unique properties and functions. *Nat Rev Neurosci* 2016, 17:89–102. [PubMed: 26806628]
 9. Kohara K, Pignatelli M, Rivest AJ, Jung HY, Kitamura T, Suh J, Frank D, Kajikawa K, Mise N, Obata Y, et al.: Cell type-specific genetic and optogenetic tools reveal hippocampal CA2 circuits. *Nat Neurosci* 2014, 17:269–279. [PubMed: 24336151]
 10. Llorens-Martin M, Jurado-Arjona J, Avila J, Hernandez F: Novel connection between newborn granule neurons and the hippocampal CA2 field. *Exp Neurol* 2015, 263:285–292. [PubMed: 25446721]
 11. Gall C, Selawski L: Supramammillary afferents to guinea pig hippocampus contain substance P-like immunoreactivity. *Neurosci Lett* 1984, 51:171–176. [PubMed: 6083512]
 12. Cui Z, Gerfen CR, Young WS, 3rd: Hypothalamic and other connections with dorsal CA2 area of the mouse hippocampus. *J Comp Neurol* 2013, 521:1844–1866. [PubMed: 23172108]
 13. Zhang L, Hernandez VS: Synaptic innervation to rat hippocampus by vasopressin-immuno-positive fibres from the hypothalamic supraoptic and paraventricular nuclei. *Neuroscience* 2013, 228:139–162. [PubMed: 23085097]
 14. Shinohara Y, Hosoya A, Yahagi K, Ferecsko AS, Yaguchi K, Sik A, Itakura M, Takahashi M, Hirase H: Hippocampal CA3 and CA2 have distinct bilateral innervation patterns to CA1 in rodents. *Eur J Neurosci* 2012, 35:702–710. [PubMed: 22339771]
 15. Sloviter RS, Sollas AL, Barbaro NM, Laxer KD: Calcium-binding protein (calbindin-D28K) and parvalbumin immunocytochemistry in the normal and epileptic human hippocampus. *J Comp Neurol* 1991, 308:381–396. [PubMed: 1865007]
 16. Herring BE, Nicoll RA: Long-Term Potentiation: From CaMKII to AMPA Receptor Trafficking. *Annu Rev Physiol* 2016, 78:351–365. [PubMed: 26863325]
 17. Simons SB, Escobedo Y, Yasuda R, Dudek SM: Regional differences in hippocampal calcium handling provide a cellular mechanism for limiting plasticity. *Proc Natl Acad Sci U S A* 2009, 106:14080–14084. [PubMed: 19666491]
 18. Lee SE, Simons SB, Heldt SA, Zhao M, Schroeder JP, Vellano CP, Cowan DP, Ramineni S, Yates CK, Feng Y, et al.: RGS14 is a natural suppressor of both synaptic plasticity in CA2 neurons and hippocampal-based learning and memory. *Proc Natl Acad Sci U S A* 2010, 107:16994–16998. [PubMed: 20837545]
 19. Shu FJ, Ramineni S, Hepler JR: RGS14 is a multifunctional scaffold that integrates G protein and Ras/Raf MAPkinase signalling pathways. *Cell Signal* 2010, 22:366–376. [PubMed: 19878719]
 - *20. Evans PR, Gerber KJ, Dammer EB, Duong DM, Goswami D, Lustberg DJ, Zou J, Yang JJ, Dudek SM, Griffin PR, et al.: Interactome Analysis Reveals Regulator of G Protein Signaling 14 (RGS14) is a Novel Calcium/Calmodulin (Ca²⁺/CaM) and CaM Kinase II (CaMKII) Binding Partner. *J Proteome Res* 2018
- This is the first demonstration for a possible link between RGS14 protein and calcium signaling. This finding may help to explain why knockout or disruption of a single regulator may ‘restore’ synaptic plasticity in CA2.

21. Evans PR, Parra-Bueno P, Smirnov MS, Lustberg DJ, Dudek SM, Hepler JR, Yasuda R: RGS14 Restricts Plasticity in Hippocampal CA2 by Limiting Postsynaptic Calcium Signaling. *eNeuro* 2018.
- *22. Carstens KE, Phillips ML, Pozzo-Miller L: Perineuronal Nets Suppress Plasticity of Excitatory Synapses on CA2 Pyramidal Neurons. *J Neurosci* 2016, 36:6312–6320.
Perineuronal nets localize to CA2 excitatory pyramidal cell somas and dendritic spines in the hippocampus. This is the first study to show that PNNs function to restrict plasticity in CA2; degrading PNNs in area CA2 in vitro enables LTP at CA2 synapses.
[PubMed: 27277807]
23. Sorg BA, Berretta S, Blacktop JM, Fawcett JW, Kitagawa H, Kwok JC, Miquel M: Casting a Wide Net: Role of Perineuronal Nets in Neural Plasticity. *J Neurosci* 2016, 36:11459–11468. [PubMed: 27911749]
24. Bruckner G, Grosche J, Hartlage-Rubsamen M, Schmidt S, Schachner M: Region and lamina-specific distribution of extracellular matrix proteoglycans, hyaluronan and tenascin-R in the mouse hippocampal formation. *J Chem Neuroanat* 2003, 26:37–50. [PubMed: 12954529]
25. Morawski M, Reinert T, Meyer-Klaucke W, Wagner FE, Troger W, Reinert A, Jager C, Bruckner G, Arendt T: Ion exchanger in the brain: Quantitative analysis of perineuronally fixed anionic binding sites suggests diffusion barriers with ion sorting properties. *Sci Rep* 2015, 5:16471. [PubMed: 26621052]
26. Hrabetova S, Masri D, Tao L, Xiao F, Nicholson C: Calcium diffusion enhanced after cleavage of negatively charged components of brain extracellular matrix by chondroitinase ABC. *J Physiol* 2009, 587:4029–4049. [PubMed: 19546165]
27. Frischknecht R, Heine M, Perrais D, Seidenbecher CI, Choquet D, Gundelfinger ED: Brain extracellular matrix affects AMPA receptor lateral mobility and short-term synaptic plasticity. *Nat Neurosci* 2009, 12:897–904. [PubMed: 19483686]
28. Klueva J, Gundelfinger ED, Frischknecht RR, Heine M: Intracellular Ca(2)(+) and not the extracellular matrix determines surface dynamics of AMPA-type glutamate receptors on aspiny neurons. *Philos Trans R Soc Lond B Biol Sci* 2014, 369:20130605. [PubMed: 25225098]
29. Piskorowski RA, Chevalayre V: Delta-opioid receptors mediate unique plasticity onto parvalbuminexpressing interneurons in area CA2 of the hippocampus. *J Neurosci* 2013, 33:14567–14578. [PubMed: 24005307]
30. Nasrallah K, Piskorowski RA, Chevalayre V: Inhibitory Plasticity Permits the Recruitment of CA2 Pyramidal Neurons by CA3. *eNeuro* 2015, 2.
31. Leroy F, Brann DH, Meira T, Siegelbaum SA: Input-Timing-Dependent Plasticity in the Hippocampal CA2 Region and Its Potential Role in Social Memory. *Neuron* 2017, 95:1089–1102.e1085. [PubMed: 28823730]
32. Evans PR, Lee SE, Smith Y, Hepler JR: Postnatal developmental expression of regulator of G protein signaling 14 (RGS14) in the mouse brain. *J Comp Neurol* 2014, 522:186–203. [PubMed: 23817783]
33. Lein ES, Hawrylycz MJ, Ao N, Ayres M, Bensinger A, Bernard A, Boe AF, Boguski MS, Brockway KS, Byrnes EJ, et al.: Genome-wide atlas of gene expression in the adult mouse brain. *Nature* 2007, 445:168–176. [PubMed: 17151600]
34. Boulanger LM, Lombroso PJ, Raghunathan A, During MJ, Wahle P, Naegle JR: Cellular and molecular characterization of a brain-enriched protein tyrosine phosphatase. *J Neurosci* 1995, 15:1532–1544. [PubMed: 7869116]
35. Ochiishi T, Saitoh Y, Yukawa A, Saji M, Ren Y, Shirao T, Miyamoto H, Nakata H, Sekino Y: High level of adenosine A1 receptor-like immunoreactivity in the CA2/CA3a region of the adult rat hippocampus. *Neuroscience* 1999, 93:955–967. [PubMed: 10473260]
36. Pelkey KA, Askalan R, Paul S, Kalia LV, Nguyen TH, Pitcher GM, Salter MW, Lombroso PJ: Tyrosine phosphatase STEP is a tonic brake on induction of long-term potentiation. *Neuron* 2002, 34:127–138. [PubMed: 11931747]
37. Noguchi A, Matsumoto N, Morikawa S, Tamura H, Ikegaya Y: Juvenile Hippocampal CA2 Region Expresses AggreCAN. *Front Neuroanat* 2017, 11:41. [PubMed: 28539874]

38. Pizzorusso T, Medini P, Berardi N, Chierzi S, Fawcett JW, Maffei L: Reactivation of ocular dominance plasticity in the adult visual cortex. *Science* 2002, 298:1248–1251. [PubMed: 12424383]
 39. Hayani H, Song I, Dityatev A: Increased Excitability and Reduced Excitatory Synaptic Input Into FastSpiking CA2 Interneurons After Enzymatic Attenuation of Extracellular Matrix. *Frontiers in Cellular Neuroscience* 2018, 12. [PubMed: 29440991]
 - *40. Piskorowski RA, Nasrallah K, Diamantopoulou A, Mukai J, Hassan SI, Siegelbaum SA, Gogos JA, Chevaleyre V: Age-Dependent Specific Changes in Area CA2 of the Hippocampus and Social Memory Deficit in a Mouse Model of the 22q11.2 Deletion Syndrome. *Neuron* 2016, 89:163–176.
- In a mouse model of 22q11.2 deletion syndrome, CA2 cellular properties and inhibitory tone are altered in postnatal development (8 weeks of age, but not 4 weeks). This is the first study to find that alterations of CA2 circuits found in neuropsychiatric disease are mimicked in a mouse genetic model.
- [PubMed: 26748091]
41. Benes FM, Kwok EW, Vincent SL, Todtenkopf MS: A reduction of nonpyramidal cells in sector CA2 of schizophrenics and manic depressives. *Biol Psychiatry* 1998, 44:88–97. [PubMed: 9646890]
 42. Zhang ZJ, Reynolds GP: A selective decrease in the relative density of parvalbumin-immunoreactive neurons in the hippocampus in schizophrenia. *Schizophr Res* 2002, 55:1–10. [PubMed: 11955958]
 43. Hensch TK: Chapter 6 - Critical Periods in Cortical Development In *The Neurobiology of Brain and Behavioral Development*. Edited by Gibb R, Kolb B: Academic Press; 2018:133–151.
 - *44. Pagani JH, Zhao M, Cui Z, Avram SK, Caruana DA, Dudek SM, Young WS: Role of the vasopressin 1b receptor in rodent aggressive behavior and synaptic plasticity in hippocampal area CA2. *Mol Psychiatry* 2015, 20:490–499.
- As a follow-up to the finding that the vasopressin 1b receptor (Avpr1b) deletion leads to reduced social aggression in mice, this study demonstrated a role for Avpr1b receptors specifically in CA2 as a regulator of this aggression. Lentiviral delivery of the Avpr1b receptor to CA2 in a knockout mouse restored aggression and Avpr1b agonists induced excitatory synaptic potentiation in CA2. The authors also reported enhancement of synaptic transmission in CA2 by vasopressin 1b and oxytocin agonists.
- [PubMed: 24863146]
45. Pagani JH, Lee HJ, Young WS, 3rd: Postweaning, forebrain-specific perturbation of the oxytocin system impairs fear conditioning. *Genes Brain Behav* 2011, 10:710–719. [PubMed: 21668734]
 46. Donaldson ZR, Young LJ: Oxytocin, vasopressin, and the neurogenetics of sociality. *Science* 2008, 322:900–904. [PubMed: 18988842]
 47. Dasgupta A, Baby N, Krishna K, Hakim M, Wong YP, Behnisch T, Soong TW, Sajikumar S: Substance P induces plasticity and synaptic tagging/capture in rat hippocampal area CA2. *Proc Natl Acad Sci U S A* 2017, 114:E8741–e8749. [PubMed: 28973908]
 48. Pedersen NP, Ferrari L, Venner A, Wang JL, Abbott SGB, Vujovic N, Arrigoni E, Saper CB, Fuller PM: Supramammillary glutamate neurons are a key node of the arousal system. *Nat Commun* 2017, 8:1405. [PubMed: 29123082]
 49. Pan WX, McNaughton N: The role of the medial supramammillary nucleus in the control of hippocampal theta activity and behaviour in rats. *Eur J Neurosci* 2002, 16:1797–1809. [PubMed: 12431233]
 50. Simons SB, Caruana DA, Zhao M, Dudek SM: Caffeine-induced synaptic potentiation in hippocampal CA2 neurons. *Nat Neurosci* 2012, 15:23–25.
 - *51. Smith AS, Williams Avram SK, Cymerblit-Sabba A, Song J, Young WS: Targeted activation of the hippocampal CA2 area strongly enhances social memory. *Mol Psychiatry* 2016

This was the first study to demonstrate a direct link between the vasopressinergic projections from the paraventricular nucleus onto CA2 neurons and behavior. Optogenetic activation of vasopressin-containing terminals in area CA2 was sufficient to enhance social memory, an effect that could be blocked with a vasopressin receptor 1b antagonist.

52. Wersinger SR, Ginns EI, O'Carroll AM, Lolait SJ, Young WS, 3rd: Vasopressin V1b receptor knockout reduces aggressive behavior in male mice. *Mol Psychiatry* 2002, 7:975–984. [PubMed: 12399951]
53. Josselyn SA, Frankland PW: Infantile amnesia: a neurogenic hypothesis. *Learn Mem* 2012, 19:423–433. [PubMed: 22904373]

Highlights:

- Pyramidal neurons in hippocampal area CA2 are morphologically and molecularly distinct from neighboring CA1 and CA3 pyramidal cells.
- Schaffer collateral synapses onto CA2 pyramidal neurons are normally resistant to the induction of synaptic plasticity.
- Plasticity can be enabled or induced in CA2 by neuromodulators such as vasopressin and caffeine, and by the deletion of negative regulators of plasticity.
- The developmental profile of several CA2-enriched molecules, such as perineuronal nets (PNNs), is highly suggestive of a critical window of plasticity in the hippocampus.

Figure 1.

Postsynaptic signaling related to plasticity differs in 'LTP-ready' CA1 and 'LTP-resistant' CA2 pyramidal neurons. Illustrated are the signaling molecules highly expressed in CA2 shown or predicted to influence LTP (dark blue/teal). Although NMDA receptor (NMDAR) currents are comparable between CA1 and CA2 [6], the calcium increases are severely limited in CA2 spines, possibly by PCP4 and RGS14, which are both highly expressed in CA2 [17,21]. Note that there is no evidence that plasma membrane calcium ATPases (PMCA) are higher in CA2. In addition, ERK/MAP kinase (ERK)-signaling is likely to be reduced by Striatal Enriched Phosphatase (STEP), which has been shown to inhibit LTP [36]. Also enriched in CA2 are the adenosine A1 receptors (A1R), which can block both LTP and adenylyl cyclases (AC), several of which are highly expressed in CA2 (1, 5, and 6; ABA [33]). Shown as a comparison, AC 2 and 8 are high in CA1, and AC 9 is highly expressed in both. Inhibition of A1Rs with caffeine or other A1R antagonists can induce synaptic potentiation that differs mechanistically from LTP [50]. Both the vasopressin 1b receptor (avpr1b; V1b) and oxytocin receptors (Oxtr) are highly expressed in CA2 pyramidal neurons and their activation can induce potentiation that appears to be mechanistically similar to LTP in its dependence on calcium (Ca^{2+}) and calcium and calmodulin dependent protein kinase II (CaMKII; [*44]). Finally, perineuronal nets (PNNs, indicated by teal hatching) surround excitatory synapses at dendritic spines in CA2 and inhibit LTP there [*22]. Dashed lines indicate possible links.

a) PCP4 mRNA

b) RGS14 protein

c) PNNs, Wisteria floribunda agglutinin

Figure 2.

Several molecules highly enriched in CA2 develop postnatally in mouse, suggestive of a critical period for LTP. Examples include a, b) PCP4 and RGS14 mRNA, ABA [33], and c) perineuronal nets (PNNs), stained with Wisteria floribunda agglutinin [*22]. Others not shown include STEP and V1b.