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Review article

Deregulation of synaptic plasticity in autism

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ABSTRACT

A puzzling observation in the study of autism spectrum disorder (ASD) in mouse models has been the deregulation of long-term synaptic depression (LTD), a form of experience-dependent synaptic plasticity, across brain areas and across syndromic and non-syndromic forms of autism. This review attempts to approach this phenomenon from a largely, but not exclusively, cerebellar perspective. Three potential consequences of LTD deregulation are discussed that are relevant for ASD phenotypes: resulting impairment of proper developmental synaptic pruning, impairment of motor coordination and motor learning, and impairment of the processing of sensory input.

1. Introduction

Synaptopathies play an important role in brain developmental disorders such as autism [1–3]. While various abnormalities in basal synaptic transmission and in plasticity have been described in ASD mouse models, deregulation of LTD is a recurring finding [4]. This is particularly evident in syndromic forms of autism. LTD deregulation has been found in mouse models for Fragile X syndrome (*Fmr1* knockout; hippocampus: [5]; cerebellum: [6]) as well as mouse models for Tuberous Sclerosis ($Tsc2^{+/-}$, hippocampus, [7]). Moreover, impaired cerebellar LTD has been found in a mouse model for the human 15q11-13 duplication (Dup15q syndrome, patDp/+ mice; [8]). LTD deregulation has also been observed for non-syndromic autism, in neuroligin-3 knockout mice (cerebellum, [9]), although the case for non-syndromic autism is weaker as cerebellar LTD was described as intact in neuroligin 1, 2, 3 triple knockouts [10], and cerebellar LTD is intact in *Shank2* knockout mice [11,12]. In all cases listed, LTD is enhanced or saturated, with the exception of $Tsc2^{+/-}$ mice [7] and patDp/+ mice [8], where LTD is reduced/prevented. As will be discussed below, under some circumstances LTD reduction and saturation can have similar consequences as even the latter will affect the dynamic range of plasticity, while in other conditions specific consequences can be described.

An inspection of genetic aberrations in syndromic forms of autism reveals a remarkable convergence on signaling pathways involved in protein translation, which are triggered by the activation of group I metabotropic glutamate receptors (mGluRs) and the subsequent activation of mammalian target of rapamycin (mTOR) signaling (for review, see [13–15]). Group I mGluRs (mGluR1 and mGluR5) initiate local mRNA translation [16]. The molecular pathway triggered by group I mGluRs that leads to enhanced cap-dependent translation is regulated by several proteins affected in various forms of syndromic autism, including TSC1/2 and FMRP (Fragile X Mental Retardation Protein; see 'mGluR theory of Fragile X syndrome', [17,18]). Together with its binding partner CYFIP1 (Cytoplasmic FMRP interacting protein 1) FMRP regulates the ability of the cap-binding translation factor eIF4E to initiate translation. *CYFIP1* is located in the proximal BP1-BP2 interval on chromosome 15q11-13, and has been shown to be upregulated in postmortem tissue from Dup15q syndrome patients [19]. Overexpression of eIF4E in transgenic mice causes ASD-like behavioural phenotypes as well as enhanced LTD in the hippocampus and striatum [20]. These findings suggest that altered translation can cause synaptic abnormalities associated with autism, including LTD deregulation. Mutations affecting TSC1/2 and FMRP signaling seem to have opposing effects on translation of synaptic (incl. LTD-relevant) proteins, but both cause autism and intellectual disability [7]. Similarly, it has recently been shown that both up- and downregulation of mTOR signaling impairs the learning of tutor songs in songbirds [21], which shows resemblance to vocal communication in humans. These findings indicate that mRNA translation, particularly that controlling local, dendritic synthesis of synaptic proteins, needs to be properly regulated and balanced, and that all deviations from this balance can have catastrophic consequences for synapse and circuit function. It is likely that LTD-regulating proteins only provide a small subgroup of important proteins that are affected, but LTD deregulation is consistently found in ASD mouse models and is therefore at the core of these considerations.

2. LTD and developmental synaptic pruning

Autism is not primarily considered as a learning disorder, because intellectual disability (with the exception of high-functioning autism)

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and behavioural abnormalities dominate the clinically relevant symptoms. Nevertheless, learning-related phenotypes can provide important leads to synapse and circuit alterations that affect brain function. The possibly most important way that learning-related synaptic abnormalities show in autism is in developmental synapse pruning. As described by Peter Huttenlocher at the University of Chicago in the early '90s, early brain development is characterized by dramatic changes in synaptic connectivity. In the human cortex synaptic density rises during the first 1–2 years after birth, followed by competitive and activity-dependent elimination of synapses that reduces the density of synaptic connections by about 50% [22]. This prolonged pruning process is crucial for proper development of brain circuits and cognitive functions. In autism, synapse/spine pruning is impaired [23], a process that is related to altered mTOR signaling [24]. Impaired synaptic pruning might well play a key role in autism as it might lead to changes in the excitation-inhibition balance and hyperexcitability ("Intense World Syndrome"; [25]) and cognitive impairment [26]. As we have recently pointed out, the molecular pathways involved in synaptic pruning are largely identical to those needed for the induction of LTD [4]. At cerebellar synapses both processes require the activation of an mGluR1/Gαq/PLCβ4/PKC signaling cascade as well as the activation of CaMKII. An overlap in molecular machinery can similarly be demonstrated at retinogeniculate synapses [27], at the neuromuscular junction and in the visual cortex [4]. In addition, it has been shown that LTD can be followed by synapse elimination, demonstrating temporal continuity and overlap [28,29]. Together, these observations suggest that LTD-like processes are involved in synaptic pruning. Thus, LTD deregulation in autism may primarily manifest as deficits in developmental synaptic pruning and the optimization of connectivity in the cerebral cortex and other areas of the brain. As synaptic plasticity is often followed by morphological changes affecting the shape or density of spines [30], abnormalities in spine pruning can be associated with deficits in synaptic pruning. However, it needs to be pointed out that synaptic and spine plasticity are not the same, and can occur independently from each other [31].

3. LTD and motor coordination/learning

ASD patients show abnormalities in delay eyeblink conditioning [32–34], a form of motor learning that requires an intact cerebellum [35]. A partial impairment of classical conditioning has also been described in ASD mouse models, including mouse models of Fragile X syndrome [6], Dup15q syndrome [8] as well as mouse models for Tuberous Sclerosis and Rett Syndrome [36], although the specific nature of the impairment may vary. When tested in the same studies, LTD at cerebellar parallel fiber (PF) to Purkinje cell synapses was described as abnormal [6,8]. LTD is seen as one of several plasticity mechanisms involved in this form of motor learning [37–39]. It is thus plausible to explain the impairment of delay eyeblink conditioning by LTD deregulation. A causal relationship is particularly supported by the finding in patDp/+ mice that re-acquisition of conditioned responses (CRs) is normal after successful CR extinction, and that LTD induction is normal after prior induction of long-term potentiation (LTP) [8]. This finding is in line with the interpretation that bidirectional synaptic plasticity at PF synapses – controlled by CF-evoked calcium transients in dendritic spines [40] – provides an important cellular correlate of some aspects of CR acquisition and extinction [41, see also 42]. It has to be noted, however, that delay eyeblink conditioning can be affected without an obvious deregulation of LTD (in *Shank2* knock-out mice; [12]). In this study, LTD was intact, but LTP and Purkinje cell intrinsic plasticity [43] were impaired. These results suggest that general disturbances of bidirectional plasticity may affect motor learning, as well as impairment of the ability to intrinsically modulate excitability in the dendrites [44] and/or neuronal spike output patterns, such as spike pauses [45, see also 46, 47].

About 80 percent of children with autism show motor impairment, including general clumsiness and problems with eye movement control [48–51]. In contrast to some of these motor problems impairment of eyeblink conditioning is a deficit that only shows when experimentally tested, and thus does not represent a daily life burden. The value of this motor learning test lies elsewhere: first, eyeblink conditioning may serve as an early biomarker for autism, allowing for quantitative analyses at ages where this is difficult to achieve based solely on social communication skills [34]. Second, eyeblink conditioning is conserved throughout mammalian evolution [52], thus allowing for direct comparisons between ASD-related behavioural symptoms/phenotypes in human patients and experimental animals.

4. LTD and processing of sensory information

Delay eyeblink conditioning is a prototype of learning of the association between two sensory stimuli, such as a light or auditory signal on the one hand and typically a periocular airpuff on the other. It seems plausible that such associative learning does not only occur in the context of protective motor behaviors, but can be used to form spatial and temporal associations between any two kinds of sensory input. In case of cerebellar forms of associative learning, the enormously large number of granule cell inputs (granule cells provide 50–80% of all neurons in the brain) and of PF – Purkinje cell synapses (up to 250,000 PF synaptic inputs target each Purkinje cell) provides a neural network that is well-suited for the storage of large numbers of associative 'memories'. In this scenario, the cerebellum indeed becomes a brain area for sensory processing, and functions in motor control become one of several consequences of cerebellar computation, solely depending on the anatomical organization of cerebellar output structures [53]. Several lines of evidence support the view that cerebellar associative learning – and thus underlying plasticity mechanisms including LTD – plays a role in associative learning beyond motor control. First, Purkinje cells respond to a wide range of sensory modalities. Next to the visual and auditory stimuli used in eyeblink conditioning, they respond to tactile body and whisker stimulation [54,55] and, in electric fish, Purkinje-like cells in the electrosensory lobe (ELL) respond to electric signals [56]. Thus, the cerebellar cortex receives and processes sensory information from multiple modalities, which can be related in a context-dependent manner in associative learning. Second, the known functions of the cerebellum and cerebellum-like structures in the weakening of predicted sensory input (involving LTD as an underlying mechanism; [57–60]) as well as in the perception of time intervals [61,62] provide examples of primarily non-motor, learning-related computations in the cerebellar cortex. It is likely that cerebellar dysfunction contributes to specific ASD symptoms/phenotypes by affecting cortical maturation during development ('developmental diaschisis'; [63]), but also because such cerebellar computations play some role in cognitive functions throughout lifetime. Whether cerebellar deficits in autism affect mental functions [64–66], non-motor language control [67] and/or social behaviors [68, see also 69] remains to be determined.

5. Conclusion

LTD deregulation in autism is a phenomenon, whose relevance for ASD phenotypes is not immediately obvious. It is well established that LTD is crucial for synaptic weight regulation and 'synaptic memories' [70], which is a process that – similar to synaptic connectivity changes during development – is essential for 'wiring plasticity' (it now seems that activity-dependent changes in intrinsic excitability provide the mechanism for the integration of neurons into memory engrams; [71]). In this review, I argue that it is the role of LTD in wiring plasticity that explains its relevance in autism. LTD deregulation prevents proper associative learning, which is most evident in the impairment of motor learning in autistic patients and ASD mouse models, and might similarly prevent proper processing of sensory inputs. However, the most

devastating effect of abnormal LTD pathways is the consequence for developmental synaptic pruning, a process that relies on a largely identical molecular machinery as LTD, and will therefore be co-impaired with LTD in the cerebellum, the cerebral cortex and likely in additional brain areas [4].

Disclosure

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References

[1] H.Y. Zoghbi, Postnatal neurodevelopmental disorders: meeting at the synapse? Science 302 (2003) 826–830.
[2] S.G. Grant, Synaptopathies: diseases of the synaptome, Curr. Opin. Neurobiol. 22 (2012) 522–529.
[3] H.Y. Zoghbi, M.F. Bear, Synaptic dysfunction in neurodevelopmental disorders associated with autism and intellectual disabilities, Cold Spring Harb. Perspect. Biol. 4 (2012) a009886.
[4] C. Piochon, M. Kano, C. Hansel, LTD-like molecular pathways in developmental synaptic pruning, Nat. Neurosci. 19 (2016) 1299–1310.
[5] K.M. Huber, S.M. Gallagher, S.T. Warren, M.F. Bear, Altered synaptic plasticity in a mouse model of fragile X mental retardation, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 7746–7750.
[6] S.K. Koekkoek, et al., Deletion of *FMR1* in Purkinje cells enhances parallel fiber LTD, enlarges spines, and attenuates cerebellar eyelid conditioning in Fragile X syndrome, Neuron 47 (2005) 339–352.
[7] B.D. Auerbach, E.K. Osterweil, M.F. Bear, Mutations causing syndromic autism define an axis of synaptic pathophysiology, Nature 480 (2011) 63–68.
[8] C. Piochon, et al., Cerebellar plasticity and motor learning deficits in a copy-number variation mouse model of autism, Nat. Commun. 5 (2014) 5586.
[9] S.J. Baudouin, et al., Shared synaptic pathophysiology in syndromic and non-syndromic rodent models of autism, Science 338 (2012) 128–132.
[10] B. Zhang, et al., Neuroligins sculpt cerebellar Purkinje-cell circuits by differential control of distinct classes of synapses, Neuron 87 (2015) 781–796.
[11] S. Ha, et al., Cerebellar Shank2 regulates excitatory synapse density, motor coordination, and specific repetitive and anxiety-like behaviors, J. Neurosci. 36 (2016) 12129–12143.
[12] S. Peter, et al., Dysfunctional cerebellar Purkinje cells contribute to autism-like behavior in Shank2-deficient mice, Nat. Commun. 7 (2016) 12627.
[13] S.J. Baudouin, Heterogeneity and convergence: the synaptic pathophysiology of autism, Eur. J. Neurosci. 39 (2014) 1107–1113.
[14] E. Santini, E. Klann, Reciprocal signaling between translational control pathways and synaptic proteins in autism spectrum disorders, Sci. Signal. 7 (2014) re10.
[15] K.M. Huber, E. Klann, M. Costa-Mattioli, R.S. Zukin, Dysregulation of mammalian target of rapamycin signaling in mouse models of autism, J. Neurosci. 35 (2015) 13836–13842.
[16] I.J. Weiler, W.T. Greenough, Metabotropic glutamate receptors trigger postsynaptic protein synthesis, Proc. Natl. Acad. Sci. U. S. A. 90 (1993) 7168–7171.
[17] M.F. Bear, K.M. Huber, S.T. Warren, The mGluR theory of fragile X mental retardation, Trends Neurosci. 27 (2004) 370–377.
[18] E.K. Osterweil, D.D. Krueger, K. Reinhold, M.F. Bear, Hypersensitivity to mGluR5 and ERK1/2 leads to excessive protein synthesis in the hippocampus of a mouse model of Fragile X syndrome, J. Neurosci. 30 (2010) 15616–15627.
[19] A. Oguro-Ando, et al., Increased CYFIP1 dosage alters cellular and dendritic morphology and dysregulates mTOR, Mol. Psychiatry 20 (2015) 1069–1078.
[20] E. Santini, et al., Exaggerated translation causes synaptic and behavioural aberrations associated with autism, Nature 493 (2013) 411–415.
[21] S. Ahmadianteherani, S.E. London, Bidirectional manipulation of mTOR signaling disrupts socially mediated vocal learning in juvenile songbirds, Proc. Natl. Acad. Sci. U. S. A. 114 (35) (2017) 9463–9468, http://dx.doi.org/10.1073/pnas.1701829114.
[22] P.R. Huttenlocher, Morphometric study of human cerebral cortex development, Neuropsychologia 28 (1990) 517–527.
[23] J.J. Hutsler, H. Zhang, Increased dendritic spine densities on cortical projection neurons in autism spectrum disorders, Brain Res. 1309 (2010) 83–94.
[24] G. Tang, et al., Loss of mTOR-dependent macroautophagy causes autistic-like synaptic pruning deficits, Neuron 83 (2014) 1131–1143.
[25] H. Markram, T. Rinaldi, K. Markram, The intense world syndrome – an alternative hypothesis for autism, Front. Neurosci. 1 (2007) 77–96.
[26] Y. Ramiro-Cortes, A.F. Hobbiss, I. Israely, Synaptic competition in structural plasticity and cognitive function, Philos. Trans. Royal Soc. B 369 (2013) 20130157.
[27] H. Lee, et al., Synapse elimination and learning rules co-regulated by MHC class I H2-D^{b}, Nature 509 (2014) 195–200.
[28] J.S. Wiegert, T.G. Oertner, Long-term depression triggers the selective elimination of weakly integrated synapses, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) e4510–4519.
[29] W. Wang, et al., Distinct cerebellar engrams in short-term and long-term motor learning, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) e194–e202.
[30] R. Yuste, T. Bonhoeffer, Morphological changes in dendritic spines associated with long-term synaptic plasticity, Annu. Rev. Neurosci. 24 (2001) 1071–1089.
[31] A.D. Sdrulla, D.J. Linden, Double dissociation between long-term depression and dendritic spine morphology in cerebellar Purkinje cells, Nat. Neurosci. 10 (2007) 546–548.
[32] L.L. Sears, P.R. Finn, J.E. Steinmetz, Abnormal classical eye-blink conditioning in autism, J. Autism Dev. Disord. 24 (1994) 737–751.
[33] J. Oristaglio, et al., Children with autism spectrum disorders show abnormal conditioned response timing on delay, but not trace, eyeblink conditioning, Neuroscience 248 (2013) 708–718.
[34] J.P. Welsh, J. Oristaglio, Autism and classical eyeblink conditioning: performance changes of the conditioned response related to autism spectrum disorder diagnosis, Front. Psychiatry 7 (2016) 137.
[35] D.A. McCormick, R.F. Thompson, Cerebellum: essential involvement in the classically conditioned eyelid response, Science 223 (1984) 296–299.
[36] A.D. Kloth, et al., Cerebellar associative sensory learning defects in five mouse autism models, eLife 4 (2015) e06085.
[37] Z. Gao, B.J. van Beugen, C.I. De Zeeuw, Distributed synergistic plasticity and cerebellar learning, Nat. Rev. Neurosci. 13 (2012) 619–635.
[38] J.H. Freeman, Cerebellar learning mechanisms, Brain Res. 1621 (2015) 260–269.
[39] M.M. ten Brinke, et al., Evolving models of Pavlovian conditioning: cerebellar cortical dynamics in awake behaving mice, Cell Rep. 13 (2015) 1977–1988.
[40] C. Piochon, et al., Calcium threshold shift enables frequency-independent control of plasticity by an instructive signal, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) 13221–13226.
[41] H. Jörntell, C. Hansel, Synaptic memories upside down: bidirectional plasticity at cerebellar parallel fiber – Purkinje cell synapses, Neuron 52 (2006) 227–238.
[42] H.K. Titley, C. Hansel, Asymmetries in cerebellar plasticity and motor learning, Cerebellum 15 (2016) 87–92.
[43] A. Belmeguenai, et al., Intrinsic plasticity complements long-term potentiation in parallel fiber input gain control in cerebellar Purkinje cells, J. Neurosci. 30 (2010) 13630–13643.
[44] G. Ohtsuki, C. Piochon, J.P. Adelman, C. Hansel, SK2 channel modulation contributes to compartment-specific dendritic plasticity in cerebellar Purkinje cells, Neuron 75 (2012) 108–120.
[45] G. Grasselli, et al., Activity-dependent plasticity of spike pauses in cerebellar Purkinje cells, Cell Rep. 14 (2016) 2546–2553.
[46] F. Johansson, H.A. Carlsson, A. Rasmussen, C.H. Yeo, G. Hesslow, Activation of a temporal memory in Purkinje cells by the mGluR7 receptor, Cell Rep. 13 (2015) 1741–1746.
[47] D.A. Jirenhed, G. Hesslow, Are Purkinje cell pauses drivers of classically conditioned blink responses? Cerebellum 15 (2016) 526–534.
[48] D. Green, et al., Impairment in movement skills of children with autistic spectrum disorders, Dev. Med. Child Neurol. 51 (2009) 311–316.
[49] K.A. Fournier, C.J. Hass, S.K. Naik, N. Lodha, J.H. Cauraugh, Motor coordination in autism spectrum disorders: a synthesis and meta-analysis, J. Autism Dev. Disord. 40 (2010) 1227–1240.
[50] B.P. Johnson, N. Rinehart, O. White, L. Millist, J. Fielding, Saccade adaptation in autism and Asperger's disorder, Neuroscience 243 (2013) 76–87.
[51] M.W. Mosconi, et al., Saccade adaptation abnormalities implicate dysfunction of cerebellar-dependent learning mechanisms in autism spectrum disorders (ASD), PLoS One 8 (2013) e63709.
[52] M.S. Fanselow, A.M. Poulos, The neuroscience of mammalian associative learning, Annu. Rev. Psychol. 56 (2005) 207–234.
[53] J.M. Bower, Is the cerebellum sensory for motor's sake, or motor for sensory's sake: the view from whiskers of a rat? Prog. Brain Res. 114 (1997) 463–496.
[54] W.T. Thach, Somatosensory receptive fields of single units in cat cerebellar cortex, J. Neurophysiol. 30 (1967) 675–696.
[55] L.W. Bosman, et al., Encoding of whisker input by cerebellar Purkinje cells, J. Physiol. 588 (2010) 3757–3783.
[56] C.C. Bell, V. Han, N.B. Sawtell, Cerebellum-like structures and their implications for cerebellar function, Annu. Rev. Neurosci. 31 (2008) 1–24.
[57] C.C. Bell, V. Han, Y. Sugawara, K. Grant, Synaptic plasticity in a cerebellum-like structure depends on temporal order, Nature 387 (1997) 278–281.
[58] C.C. Bell, Memory-based expectations in electrosensory systems, Curr. Opin. Neurobiol. 11 (2001) 481–487.
[59] V.Z. Han, Y. Zhang, C.C. Bell, C. Hansel, Synaptic plasticity and calcium signaling in Purkinje cells of the central cerebellar lobes of mormyrid fish, J. Neurosci. 27 (2007) 13499–13512.
[60] N.B. Sawtell, Multimodal integration in granule cells as a basis for associative plasticity and sensory prediction in a cerebellum-like circuit, Neuron 66 (2010) 573–584.
[61] M.J. Allman, S. Teki, T.D. Griffiths, W.H. Meck, Properties of the internal clock: first – and second-order principles of subjective time, Annu. Rev. Psychol. 65 (2014) 743–771.
[62] S. Teki, T.D. Griffiths, Brain bases of working memory for time intervals in rhythmic sequences, Front. Neurosci. 10 (2016) 239.
[63] S.S.H. Wang, A.D. Kloth, A. Badura, The cerebellum, sensitive periods, and autism, Neuron 83 (2014) 518–532.
[64] J.D. Schmahmann, An emerging concept: the cerebellar contribution to higher function, Arch. Neurol. 48 (1991) 1178–1187.
[65] M. Ito, Movement and thought: identical control mechanisms by the cerebellum, Trends Neurosci. 16 (1993) 448–450.
[66] M. Ito, Control of mental activities by internal models in the cerebellum, Nat. Rev. Neurosci. 9 (2008) 304–313.
[67] H.C. Leiner, A.L. Leiner, R.S. Dow, Cognitive and language functions of the human

cerebellum, Trends Neurosci. 16 (1993) 444–447.
[68] P.T. Tsai, et al., Autistic-like behavior and cerebellar dysfunction in Purkinje cell Tsc1 mutant mice, Nature 488 (2012) 647–651.
[69] E. Galliano, et al., Synaptic transmission and plasticity at inputs to murine cerebellar Purkinje cells are largely dispensable for standard nonmotor tasks, J. Neurosci 33 (2013) 12599–12618.
[70] C. Hansel, M.F. Bear, LTD – synaptic depression and memory storage, In Molecular mechanisms of memory, in: J.D. Sweatt, J. Byrne (Eds.), Vol. 4 of Learning and Memory: a Comprehensive Reference, Elsevier, Oxford, 2008, pp. 327–366.
[71] H.K. Titley, N. Brunel, C. Hansel, Toward a neurocentric view of learning, Neuron 95 (2017) 19–32.