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Heterosynaptic Plasticity in Cortical Interneurons

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Review of Chistiakova et al.

Persistent alteration of synaptic strength in response to neuronal activity has long been considered a substrate of learning and memory (Hebb, 1949). Classical Hebbian plasticity results from near-coincident presynaptic and postsynaptic action potentials (APs), with the precise order of spiking, either pre-post or post-pre, yielding an increase (LTP) and a decrease (LTD) of synaptic weights, respectively (Hebb, 1949; Bliss and Lomo, 1973; Levy and Steward, 1983; Malenka and Nicoll, 1993; Markram et al., 1997). When input-specific, this type of synaptic plasticity is referred to as homosynaptic plasticity. Hebbian forms of plasticity are central to cellular models of learning, but it presents a fundamental problem regarding the stability of neural networks. Specifically, unconstrained LTP expression may produce a pernicious positive-feedback loop and runaway excitation, whereas LTD can lead to extreme depression and synaptic demise.

Two forms of plasticity have been proposed to solve the network stability problem and counteract runaway dynamics that might otherwise arise with homosynaptic LTP and LTD: homeostatic plasticity

(Lee et al., 2014) and some forms of heterosynaptic plasticity (Royer and Paré, 2003). Heterosynaptic plasticity occurs at synaptic connections not activated by the presynaptic neuron and therefore does not exhibit strict input specificity (unlike Hebbian plasticity). In some cases, the polarity of heterosynaptic plasticity leads to synaptic weight normalization (Royer and Paré, 2003) and thus contributes to network stabilization. Heterosynaptic plasticity has been reported mainly in synaptic connections between excitatory neurons. In a recent paper published in *The Journal of Neuroscience*, Chistiakova et al. (2019) investigated the presence of heterosynaptic plasticity at synapses between excitatory and inhibitory neurons of the visual cortex of young male rats.

The authors used extracellular electrodes to stimulate two sets of excitatory inputs onto a single inhibitory neuron whose activity was monitored in whole-cell intracellular recordings. Classic homosynaptic plasticity was induced at one set of inputs by pairing each of 30 excitatory presynaptic spikes with 5 postsynaptic APs (paired input). The second set of excitatory inputs was not activated during postsynaptic APs (unpaired input), thereby allowing the authors to monitor the presence of heterosynaptic plasticity at these synapses. This protocol induced mixed plasticity (i.e., LTP, LTD, or no change) at both paired and unpaired inputs. Precisely, if the paired input yielded LTD in a given neuron, the unpaired input onto that same neuron could express LTP or LTD. These results provided evidence of

heterosynaptic plasticity. The authors then showed that activating the postsynaptic neuron with 30 bursts of 5 APs, in the absence of any presynaptic stimulation, was sufficient to induce heterosynaptic plasticity at excitatory inputs, again of mixed polarity. These results therefore hint toward a postsynaptic site of induction for this plasticity mechanism, leaving unanswered the site of expression.

Chistiakova et al. (2019) proceeded to examine whether cell type could account for the plasticity variability observed. They classified the recorded cells as fast-spiking (FS) or non-FS neurons, the two major classes of cortical inhibitory neurons (Kawaguchi and Kubota, 1997). Burst firing alone in FS neurons, without concurrent synaptic stimulation, induced mixed synaptic weight modifications: LTP (32%), LTD (34%), or no change (34%). These proportions are similar to those previously reported for excitatory synapses onto pyramidal neurons undergoing a similar protocol (Volgushev et al., 2016). Remarkably, excitatory synapses onto non-FS neurons responded differently in that they were preferentially potentiated (47%) in response to postsynaptic bursts alone, with only 15% of synapses expressing LTD and 38% expressing no change. Synapses onto non-FS neurons averaged $116 \pm 4.9\%$ potentiation compared with $106 \pm 3.7\%$ in FS neurons. Collectively, these results demonstrated important differences in the direction of heterosynaptic plasticity between interneuron subtypes.

The authors then examined mechanisms that might account for these differences.

Received Oct. 27, 2019; revised Jan. 22, 2020; accepted Jan. 27, 2020.

The author is a trainee in the laboratory of Dr. Jean-Claude Béique who is supported by the Natural Sciences and Engineering Research Council of Canada and the Canadian Institutes of Health Research. I thank Dr. Béique and laboratory members for the ongoing training and exciting discussion that continuously shapes my research interests and professional development; and Philippe Vincent-Lamarre for providing useful comments.

The author declares no competing financial interests.

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<https://doi.org/10.1523/JNEUROSCI.2567-19.2020>

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Specifically, they looked for predictors of the direction of plasticity, focusing on animal age, cortical layer, initial release probability, as well as baseline EPSP amplitude, latency, and slope. Of these, the initial release probability of synapses (determined by the ratio of a 50 ms interval paired-pulse) was found to be the strongest predictor of plasticity direction: synapses with initial low release probability (high paired-pulse ratio [PPR]) were more likely to undergo LTP, whereas those with high release probability (low PPR) tended to undergo LTD. The relationship between initial PPR and the sign of plasticity suggests a weight-dependent heterosynaptic plasticity, which favors the hypothesis that heterosynaptic plasticity can act to normalize synaptic weights. This is because synapses with low release probability are relatively unlikely to respond to a single stimulus. These weak synapses tend to be reinforced by this form of LTP, whereas synapses with high release probability are more likely to be depressed. As a result, the total synaptic weight tends to be largely unchanged, thereby enacting a form of weight normalization. Importantly, synapses onto non-FS neurons on average had lower release probability than those onto FS neurons, which may explain the enhanced propensity of synapses onto non-FS neurons to potentiate.

The results outlined above do not formally address the site of expression of this form of plasticity. To this end, Chistiakova et al. (2019) further dissected the relationship between the release probability of the synapse and the direction of heterosynaptic plasticity. The authors found that, even during strictly postsynaptic activation, heterosynaptic LTP was mediated at least partly by an increase in release probability, whereas LTD was mediated by a decrease in release probability. These results indicate that, although the plasticity is induced by postsynaptic spiking alone, it is mediated by presynaptic changes. Such plasticity would necessarily require trans-synaptic interactions. This interaction could be mediated by postsynaptic release of a retrograde messenger that activates presynaptic receptors after strong postsynaptic depolarization (Zilberter et al., 1999). Multiple retrograde messengers have been shown to induce long-term changes in synaptic weights by modifying presynaptic release probability (Zilberter et al., 1999; Nugent et al., 2007). Chistiakova et al. (2019) discussed nitric oxide as a possible candidate (Volgushev et al., 2000), although more than one retrograde messenger may be involved. Another possibility is that GABA is dendritically released

from the postsynaptic neuron and acts on GABA_B receptors located on the presynaptic terminal of excitatory neurons (Zilberter et al., 1999; Gonchar et al., 2001). Indeed, GABA_B receptors are present at the presynaptic extracellular synaptic sites of excitatory neurons of the visual cortex (Gonchar et al., 2001). In other cell types, activation of GABA_B receptors at the presynaptic terminal has been shown to suppress the activity of voltage-sensitive calcium channels and thus reduce glutamate release onto several cell types (Dolphin and Scott, 1986; Gonchar et al., 2001; Geddes et al., 2016). Determining which retrograde messengers are involved is imperative to determining the mechanism enabling the presynaptically expressed heterosynaptic plasticity observed by Chistiakova et al. (2019).

Another important question is how the heterosynaptic plasticity observed here is determined by the initial release probability of the synapse. The interaction of retrograde messengers with specific receptors at the presynaptic membrane has been shown, in some cases, to yield presynaptic LTP or LTD (Pelkey et al., 2005). In this way, receptors may be upregulated and downregulated according to the state of the synapse, and allow retrograde signaling to modify the synaptic weight accordingly (Crosby et al., 2011). Alternatively, proteins such as protein kinase C, whose activity regulates the size of the readily releasable pool of vesicles (Stevens and Sullivan, 1998), which correlates with synaptic release probability (Dobrunz, 2002), could mediate the effects of the retrograde signal. Future research will be required to dissect the mechanism underlying the weight dependence of heterosynaptic plasticity as a means to implement synaptic weight normalization.

The study of Chistiakova et al. (2019) supports the generality of heterosynaptic plasticity and supports the hypothesis that this form of plasticity helps to stabilize total synaptic weights. Future work, likely relying in part on computational modeling of neural networks, is necessary to determine how homeostatic plasticity and weight-dependent heterosynaptic plasticity mechanisms at both presynaptic and postsynaptic sites interact to maintain neural network stability.

References

- Bliss TV, Lomo T (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J Physiol* 232:331–356.
- Chistiakova M, Ilin V, Roshchin M, Bannon N, Malyshev A, Kisvárdy Z, Volgushev M (2019)

Distinct heterosynaptic plasticity in fast spiking and non-fast-spiking inhibitory neurons in rat visual cortex. *J Neurosci* 35:6865–6878.

Crosby KM, Inoue W, Pittman QJ, Bains JS (2011) Endocannabinoids gate state-dependent plasticity of synaptic inhibition in feeding circuits. *Neuron* 71:529–541.

Dobrunz LE (2002) Release probability is regulated by the size of the readily releasable vesicle pool at excitatory synapses in hippocampus. *Int J Dev Neurosci* 20:225–236.

Dolphin AC, Scott RH (1986) Inhibition of calcium currents in cultured rat dorsal root ganglion neurons by (–)-baclofen. *Br J Pharmacol* 88:213–220.

Geddes SD, Assadzadeh S, Lemelin D, Sokolovski A, Bergeron R, Haj-Dahmane S, Béique JC (2016) Target-specific modulation of the descending prefrontal cortex inputs to the dorsal raphe nucleus by cannabinoids. *Proc Natl Acad Sci U S A* 113:5429–5434.

Gonchar Y, Pang L, Malitschek B, Bettler B, Burkhalter A (2001) Subcellular localization of GABA(B) receptor subunits in rat visual cortex. *J Comp Neurol* 431:182–197.

Hebb DO (1949) The organization of behavior: a neuropsychological theory. New York: Wiley.

Kawaguchi Y, Kubota Y (1997) GABAergic cell subtypes and their synaptic connections in rat frontal cortex. *Cereb Cortex* 7:476–486.

Lee KF, Soares C, Béique JC (2014) Tuning into diversity of homeostatic synaptic plasticity. *Neuropharmacology* 78:31–37.

Levy WB, Steward O (1983) Temporal contiguity requirements for long-term associative potentiation/depression in the hippocampus. *Neuroscience* 8:791–797.

Malenka RC, Nicoll RA (1993) NMDA-receptor-dependent synaptic plasticity: multiple forms and mechanisms. *Trends Neurosci* 16:521–527.

Markram H, Lübke J, Frotscher M, Sakmann B (1997) Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* 275:213–215.

Nugent FS, Penick EC, Kauer JA (2007) Opioids block long-term potentiation of inhibitory synapses. *Nature* 446:1086–1090.

Pelkey KA, Lavezzi G, Racca C, Roche KW, McBain CJ (2005) mGluR7 is a metaplastic switch controlling bidirectional plasticity of feedforward inhibition. *Neuron* 46:89–102.

Royer S, Paré D (2003) Conservation of total synaptic weight through balanced synaptic depression and potentiation. *Nature* 422:518–522.

Stevens CF, Sullivan JM (1998) Regulation of the readily releasable vesicle pool by protein kinase C. *Neuron* 21:885–893.

Volgushev M, Balaban P, Chistiakova M, Eysel UT (2000) Retrograde signaling with nitric oxide at neocortical synapses. *Eur J Neurosci* 12:4255–4267.

Volgushev M, Chen JY, Ilin V, Goz R, Chistiakova M, Bazhenov M (2016) Partial breakdown of input specificity of STDP at individual synapses promotes new learning. *J Neurosci* 36:8842–8855.

Zilberter Y, Kaiser KM, Sakmann B (1999) Dendritic GABA release depresses excitatory transmission between layer 2/3 pyramidal and bitufted neurons in rat neocortex. *Neuron* 24:979–988.