Commentary

Serotonergic control of developmental plasticity

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Synapses in the brain are more than just coupling devices between neurons. Their efficiency in relaying neural activity can change according to their use. This plastic characteristic of synapses is considered essential for learning and memory storage and for the refinement of connections during development. A model of choice for studying synaptic modifications is the visual cortex, which shortly after birth is in a state of enhanced plasticity. During this time the cortical circuitry can be altered with simple manipulations of visual experience. For example, deprivation of vision in one eye (monocular deprivation) shifts the response of cortical neurons toward the nondeprived eye (1). It was recognized early on that in addition to the activity patterns imposed by retinal inputs, visual cortical plasticity depends on the integrity of three diffusely projecting neurotransmitter systems, using noradrenaline (NE), acetylcholine (ACh), and serotonin (5HT), respectively. These neuromodulatory systems convey information on the behavioral state of the animal, and their disruption prevents ocular dominance shifts caused by monocular deprivation (2–5). Hence, these neuromodulators have been regarded as "enabling factors" that perform the important function of gating experience-induced plasticity under certain behavioral states (6). This idea may have to be revised and expanded in view of new results recently published in PNAS (7). This study provides evidence that activation of serotonergic receptors might control not only when plasticity occurs, but also where a given input will be strengthened or weakened.

Our understanding of the mechanism by which neuromodulators affect experience-induced plasticity derives primarily from studies conducted *in vitro*, in the brain slice preparation. There is now ample evidence that ACh, NE, and 5HT can affect the induction of two forms of activity-dependent synaptic modification: long-term potentiation (LTP) and long-term depression (LTD). LTP and LTD are the most comprehensive models for synaptic strengthening and weakening, respectively. In the visual cortex, LTP and LTD can be specifically induced with distinct patterns of afferent stimulation. Brief and strong episodes of high-frequency stimulation yield LTP, whereas prolonged low-frequency stimulation induces LTD. In the presence of ACh and NE, LTP can be induced with weaker tetanic stimulation, and LTD can be induced with shorter episodes of low-frequency stimulation (8, 9). Thus, consistent with their role as enabling factors, activation of cholinergic and noradrenergic receptors lowers the threshold of activity required for the induction of LTP and LTD.

In contrast to the clear case of NE and ACh, the effects of 5HT on LTP/D have been more difficult to nail down. In cat visual cortex, the serotonergic terminals are uniformly distributed across all layers, but the 5HT receptors implicated in experience-dependent plasticity, 5HT2C, are restricted to layer IV (10). Synapses in layer IV have the capacity to express LTP and LTD shortly after birth (11–13). However, cells in this layer are strongly inhibited by GABAergic circuits, making it difficult to induce plasticity with patterned stimulation only. For example, stimulation at 1 Hz for 15 min, the standard protocol for inducing LTD, will not produce any change unless inhibition is removed (12). Therefore, this type of stimulation can be useful for testing the facilitatory effect of neuromodulators. In an early study, Cynader and colleagues (14) investigated whether 5HT will facilitate the induction of LTD. They found that activation of 5HT2C receptors did facilitate LTD with 1-Hz stimulation. However, it was only observed in about half of the attempts. In the other cases, surprisingly, serotonergic activation in conjunction with low-frequency stimulation resulted in LTP. Thus, activation of 5HT2C receptor facilitated both LTP and LTD, but in a seemingly unpredictable way.

The answer to this disparate array of results was to be found in the peculiar patchy distribution of serotoninergic receptors. In layer IV, 5HT2C localize in bands of high density interleaved with zones poor in receptors (10). This pattern is regularly repeated every 900 mm or so. The patchy distribution of 5HT receptors suggested that 5HT might preferentially facilitate LTP in one type of patch, while facilitating LTD in the other. To test this hypothesis, Kojic *et al.* (7) took advantage of the fact that this 5HT receptor patch system is complementary to another system of patches: the cytochrome oxidase (CO) blobs in layer II/III. The CO blobs in layer II/II are in register with 5HT receptor-poor patches in layer IV, whereas interblobs are on top of 5HT receptor-rich patches (15). Post hoc patch identification revealed that 5HT promoted the induction of LTP in 5HT2C receptor-rich patches and LTD in the receptor-poor patches (7). Before this study, neuromodulators were considered to determine the occurrence and the magnitude of plasticity. It is clear now that 5HT also can specify the sign of plasticity, such that LTP is induced where receptor density is high, and LTD occurs where receptor density is low.

Clearly, it is not the pattern of input activity alone that determines the sign of plasticity. The same input pattern will result in strengthening or weakening of synapses depending on the density of active postsynaptic neuromodulator receptors. Therefore, the spatial and temporal pattern of neuromodulator receptors during development can strongly shape the weakening and strengthening of inputs in the cortex. Significantly, the 5HT receptor patches only occur during the critical period for layer IV plasticity (10). The differential serotonergic facilitation of LTP and LTD in these patches might be particularly relevant to the modular organization of the visual cortex. Cells with similar physiological properties tend to cluster together in patches. One example is the CO blobs and interblob system. In cat visual cortex cells in the CO blobs are more responsive to high temporal frequencies, whereas cells in the interblobs prefer lower temporal frequencies (16). What might be the mechanism to establish this functional parcellation? The anisotropy of the serotonergic system seems

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ideally suited to promote segregation of inputs according to their patterns of activity. Upon serotonergic activation, inputs carrying low-frequency patterns of activity would undergo LTD in the layer IV regions containing a low density of 5HT2 receptors. As a consequence, low-frequency activity would not be relayed to the overlying CO blob cells. On the other hand, inputs carrying low-frequency activity would form stronger connections with the 5HT2 receptor-rich neurons in layer IV that feed information to the interblob regions. It will be of considerable interest to determine whether the serotonergic system contributes to blob/interblob functional segregation in this manner.

The mechanisms by which 5HT and the other neuromodulators facilitate LTP and LTD remain to be elucidated. In visual cortex, as in many other places, the induction of LTP and LTD requires the activation of *N*-methyl-D-aspartate (NMDA) receptors and a postsynaptic rise in intracellular calcium. The available evidence is consistent with a model in which the magnitude and duration of the calcium signal determines the sign and magnitude of the synaptic changes (17). Brief and large Ca^{2+} increases induce LTP, whereas smaller but prolonged Ca^{2+} increases lead to LTD. Thus, extracellular signals capable of modifying the intracellular Ca^{2+} levels will potentially alter the activity requirements for LTP and LTD. 5HT is such a signal, because 5HT2C receptors are coupled to the IP3 second messenger pathway, which can induce Ca^{2+} release from intracellular stores. In addition, 5HT2C receptors have been demonstrated to enhance NMDA receptor activation. Because the release of 5HT presumably is uniform throughout layer IV, the differential density of postsynaptic 5HT2C receptors is an important parameter that will determine whether the rise in intracellular Ca^{2+} reaches the threshold for inducing LTP or LTD.

In addition to 5HT2C receptors, the IP3 pathway can be activated by cholinergic (m1) receptors and noradrenergic (a1) receptors. Thus, the three major modulatory inputs to the cortex appear to use the same molecular mechanism, consistent with the idea that each neuromodulatory system (ACh, NE, and 5HT) has a similar effect on plasticity. However, although they converge into the same intracellular signaling mechanism, the three neuromodulators systems are active during different behavioral states. Only when the animal is awake and attentive, are the three systems simultaneously active (18). Temporal variations in the combinatorial activity of neuromodulators during different behavioral states might produce similar effects as spatial variations in the density of receptors. For example, a given pattern of input activity might weaken synapses when only one neuromodulatory system is on, but strengthen them when the three systems are active simultaneously. In this way, the rules of synaptic plasticity might appear different, depending on when and where one looks.

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