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Networking into neural plasticity: A rising score on the cytokine learning curve

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Ever since the discovery of inflammatory cytokines, the tentacles of cytokine actions have slowly crept beyond the boundaries of the immune system into the central nervous system (CNS) where they have unexpectedly seemed to graft onto this inflammation-averse environment. Cytokine activity can obviously be found in infected or injured CNS tissue as their traditional roles in mediating immune activity and wound healing are needed under these special circumstances. What began to intrigue were early findings that cytokines in the un-injured and un-infected CNS mediate sickness behavior and neuroendocrine activation during peripheral inflammation, indicating a neuromodulatory role for these molecules (Quan and Banks, 2007). The furthest extension for the role of cytokines is the notion that they may even be involved in normal brain physiology without precedent detectable inflammation either in the brain or in the periphery. A line of research in this regard has been pioneered by the authors of the study on cytokine network and learning in this issue of BBI (Del Rey et al., 2013), culminating to their demonstration of a cytokine network in the physiological process of learning.

Their opening salvo was the seminal demonstration of the involvement of interleukin-1 (IL-1) in long-term potentiation (LTP), an integral cellular process in many forms of learning and memory (Schneider et al., 1998). They found the expression of IL-1 is significantly increased during LTP. Furthermore, blocking IL-1 activity resulted in a reversible inhibition of LTP, whereas blocking the induction of LTP using a neurotransmitter antagonist prevented the induction of IL-1. Thus, IL-1 was shown to be induced by neuronal activity, produced from cells of the CNS, and played a role in the regulation of a cellular process that is critical in learning and memory. Importantly, IL-1 was found to support LTP in this study, whereas the opposite was found by many other studies (Deak, 2007). An explanation for this apparent dichotomy was furnished by Yirmiya et al. who suggested most studies used pathophysiological conditions to induce high levels of IL-1. High IL-1 concentrations tend to impede learning and memory, but physiological IL-1 is produced at low levels in the brain, supporting normal learning and memory processes (Yirmiya and Goshen, 2011). Indeed, distinct actions have been found for another cytokine, IL-6, which negatively influences LTP (Balschun et al., 2004) under physiological conditions, unlike the typical synergism between IL-1 and IL-6 often observed under pathophysiological conditions.

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Therefore, beyond the pale of pathophysiological actions of cytokines, which may be much easier to demonstrate due to the involvement of high levels of cytokines, multiple cytokines at low physiological levels may be involved in homeostatic learning and memory regulation through a distinct set of actions. This issue is addressed by Del Rey et al. in the current issue. They found that in addition to IL-1 β and IL-6, both IL-1ra and IL-18, but not TNF α , are also induced during LTP in vivo. All these inductions in LTPs were abrogated by an NMDA receptor antagonist. In addition, IL-1 β , IL-6, and IL-18 were induced during a hippocampal-dependent learning task in discrete regions of the hippocampus, whereas IL-1ra was reduced in the prefrontal cortex. An elegant design in this study was the inclusion of a pseudo-trained control group which was manipulated in the same apparatus without learning, ensuring the findings were truly related to the learning process. Results showed the animals' learning scores correlated positively with IL-1 β levels, but negatively with IL-1ra levels. Thus, the physiological processes of learning appear to causally engage a cytokine network. These results further support the theory that an underground cytokine network is operative under non-inflammatory conditions to modulate normal neural activity, especially the events involved in learning and memory processes.

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