Brief Commentary

From hippocampus to dorsal horn: The pervasive impact of IL-1 on learning and memory spans the length of the neuroaxis

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In 1988, Benjamin Hart published a highly influential review arguing that behavioral manifestations of acute illness were recuperative in nature and did not represent a sign of behavioral debilitation (Hart, 1988). Since that time, the expression of sickness behaviors has come to be viewed as a goal-directed (i.e., motivational) process that can be suspended when reproductive fitness is at stake (Dantzer, 2004). Moreover, advances in biochemical and molecular techniques have led to exponential growth in the detection of soluble factors (cytokines, chemokines, prostanoids, etc) that play an identifiable role in cross-talk among immune cells, endocrine systems and the CNS. Today, it is largely accepted that soluble factors more traditionally associated with peripheral immune function can serve as signaling factors within the CNS and that inflammatory signaling pathways modulate a multitude of CNS-mediated events. Of the many cytokines and immune-related factors that have been isolated, Interleukin-1 (IL-1) repeatedly emerges as a fundamental factor seemingly involved in all facets of neuroimmune and neuroinflammatory processes, ranging from fever (Kluger, 1991) to sickness behavior (Kent et al., 1992) to neuropathic pain (Watkins et al., 2001) and even consequences of stressor exposure (Deak et al., 2005).

The impact of cytokines on CNS functioning is no longer restricted to affective and motivational processes, but has naturally extended into the realm of cognition, with particular focus on learning and memory processes. Indeed, immune activation by LPS has been shown to interfere with spatial learning in the Morris water maze (Oitzl et al., 1993) as well as contextual (but not auditory-cued) fear conditioning (Pugh et al., 2001). These data guided mechanistic studies towards the hypothesis that increased IL-1 in the hippocampus produced during immune challenge can impair learning that relies largely on this structure for its expression. This hypothesis has been well-supported by empirical data at multiple levels of analysis, including findings that microinjection of IL-1 into the hippocampus produces impairments similar to immune activation (Barrientos et al., 2002) and retards the development of long-term potentiation (Lynch, 1998).

The manuscript by Young et al. (2007) extends the influence of immune activation on learning and memory to the spinal cord, and in doing so, binds together several research areas within the broader fields of psychoneuroimmunology, traumatic CNS injury and neuropathic pain. The authors employed a well-established spinal learning paradigm where spinalized rats were given the opportunity to terminate shocks by performing an instrumental (leg flexion) response. Spinalized rats readily learn this contingency and there is a growing body of literature examining the mechanisms of spinal plasticity that underly this spinal learning phenomenon (Grau et al., 2006). Interestingly, prior exposure to noncontingent shock produces a learning deficit when rats are later tested in a contingent shock paradigm, and rats can be protected against the ill-effects of noncontingent shock by prior contingent shock exposure. Double-speak aside, what this means is that prior experience with controllable shock produces a veritable resilience against the maladaptive consequences of uncontrollable shock. Indeed, these effects were borne out of the classic literature with controllable and uncontrollable stress and are reminiscent of ‘learned helplessness’ and ‘behavioral immunization’, respectively (Maier and Watkins, 2005). Recall, however, that these effects are observed in rats with full spinal transections, suggesting that spinal learning may rival the complexity that is typi-
cally only afforded to higher brain structures such as the hippocampus (for declarative and spatial learning) and the extended amygdala complex (for fear-related learning). In this regard, the spinal learning paradigm employed by Young et al. (2007) offers unique prospects for examining higher order processing at the segmental level.

Turning our attention back to the inflammation-learning interaction, the authors sought to examine whether initiation of a systemic inflammatory response by LPS would provoke impairments in spinal learning comparable to those observed in more traditional learning tasks. Interestingly, previous work had already shown that local inflammation in the foot-pad impairs the response-outcome contingency in this paradigm. Though the spinal learning deficits were only observed after a relatively high dose of LPS, responsiveness to LPS is often diminished in rats post-surgery, which can manifest as a rightward shift in the dose response curve or an increased percentage of LPS non-responders. Notably, however, the effects of LPS were highly consistent across four consecutive experiments, which speaks to excellent reproducibility. Appreciation for this effect is increased when one considers that LPS administration after exposure to contingent shock but before the noncontingent shock supplanted the protective effects of prior instrumental learning. This effect is likely due to interference with spinal memory consolidation processes produced by the intervening LPS injection, and extends what is already known about the memory-dampening effects of immune activation in hippocampally-mediated tasks (Pugh et al., 2001). The manuscript dovetails into mechanistic tests to determine the potential role for iNOS and IL-1 as signaling cascades that might underwrite the LPS-induced interference with spinal learning, where IL-1 (but not iNOS) emerged as the critical culprit once again.

A multidisciplinary approach is necessarily embedded in the field of psychoneuroimmunology, yet few of us truly span the gamut like the integrative work performed in the article by Young et al. Perhaps more importantly, this work brings to light several fundamental principles that draw my appreciation. First, the spinal cord does far more than just parlay information from periphery to brain and back again; it retains the rich powers of processing and plasticity that are too often ascribed to only higher brain centers. Second, from modulation of cognitive, motivational and affective processes to spinal plasticity in the severed cord, no site in the CNS is truly protected from the influence of immune activation. Finally, by chance or by design, IL-1 has pervasive effects on CNS functioning that truly span the length of the neuroaxis. In this regard, the work of Young and colleagues provides strident advances towards integration of seemingly disparate fields of inquiry, and will be instrumental in the development of new strategies for the treatment of spinal cord injury and neuropathic pain.

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References

Hart, B.L., 1988. Biological basis of the behavior of sick animals. Neuroscience and Biobehavioral Reviews 12, 123–137.