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HOT TOPICS

Self-administered fentanyl profoundly impacts rat brain innate immune targets

Irma E. Cisneros [1,2,3] and Kathryn A. Cunningham [1,2,4]

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Opioid overdoses and the chronic, deadly medical condition of opioid-use disorder (OUD) are escalating public health crises gripping the United States. Within the context of ever-possible overdose events, OUD is characterized by opioid-taking and opioid-seeking and evolves with expanding dysfunction in limbic–mesocorticostriatal circuitry. Neurons, astroglia, microglia, and blood-born cells comprise anatomical and reciprocal communication between the immune and nervous systems within the nodes of this circuitry. There is a great opportunity to improve our basic science understanding of neuroimmune targets involved in response to opioid exposure. This need is highlighted by observations that link opioid exposure to signatures of neuroinflammation, as well as the mixed results of candidate immune modulators in adults with opioid dependence [1].

Opioid tolerance and withdrawal are reported to disrupt immediate innate and delayed, adaptive neuroimmune signaling to foreign material, most notably described for pathogens [2]. However, much remains to be learned concerning neuroimmune function along the continuum from opioid misuse to more severe stages of OUD. Ultimately, defining mechanisms of opioid-associated innate immune dysregulation will aid in optimizing treatments for OUD at a given stage in the OUD cycle [3]. We modeled a short-access, low-dose opioid-use pattern in male rats that aligns with the initiation of opioid misuse in humans [4]. We chose an early timepoint of abstinence (24 h) which falls within the rapid response mechanisms of innate immunity and evaluated cytokines, chemokines, and other immune modulators in nodes of the limbic–mesocorticostriatal system ex vivo [4]. As an example of several intriguing findings, twofold or greater increases and decreases in key innate immune proteins were observed in the nucleus accumbens and hippocampus, respectively. Intriguingly, we discovered decreases in select cytokines (e.g., several interleukins) and the stimulator of interferon genes (STING) proteins in the hippocampus. We also uncovered particularly strong positive relationships ($R^2 > 0.80$; $P < 0.0001$) between STING and interleukin (IL) 4 and IL7 protein expression in the hippocampus. Although little is known about the role of IL7 in the hippocampus, aged mice exhibit learning defects associated with decrease hippocampal IL4 and a crucial role for IL4 in spatial learning and neurogenesis has been reported [5].

The directionality of these relationships remains to be established; however, we propose that the fentanyl-associated decrement in STING may result in a cascade of neuroimmune adaptations that serve as a novel mechanistic driver of brain immune decrements involved in initiation of opioid misuse and perhaps the development of OUD. Furthermore, our findings of fentanyl-induced CNS innate immune responses suggest that chronic opioid exposure may increase the onset and/or severity of neurocognitive disorders associated with viral brain infections via STING.

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AUTHOR CONTRIBUTIONS

IEC and KAC wrote, reviewed, and approved the final version.

ADDITIONAL INFORMATION

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[1]Center for Addiction Research, University of Texas Medical Branch, 301 University Blvd, Galveston, TX 77550, USA; [2]Institute for Human Infections and Immunity, University of Texas Medical Branch, 301 University Blvd, Galveston, TX 77550, USA; [3]Department of Pathology, University of Texas Medical Branch, 301 University Blvd, Galveston, TX 77550, USA and [4]Department of Pharmacology and Toxicology, University of Texas Medical Branch, 301 University Blvd, Galveston, TX 77550, USA
Correspondence: Irma E. Cisneros (ircisner@utmb.edu)

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