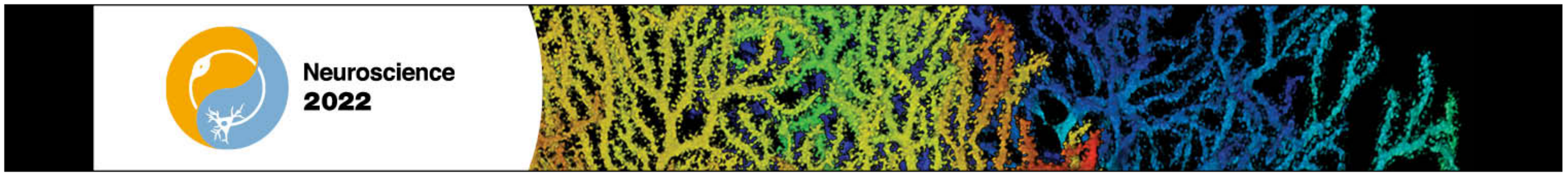

Control/Tracking Number: 2022-S-3097-SfN
Activity: Scientific Abstract
Current Date/Time: 6/13/2022 1:01:29 PM

Enhanced stress response in rats that suffered acute neuroinflammation induced by neuraminidase three months before

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Abstract:
Microglial cells are protagonists in neuroinflammatory processes and their activation is a notorious feature of such events. In acute inflammation, microglial cells return to their basal surveillant state in few days. However, sometimes they evolve towards a primed state, characterized by hypersensitivity to new stimuli and an exacerbated response which may jeopardize brain functions. Because the hypothalamus is a pivotal hub for neuroendocrine and autonomic functions, we have been exploring evidences of microglial priming in this region and its consequences. We used a model of acute ventricular neuroinflammation consisting in the intracerebroventricular (ICV) injection of neuraminidase (NA). This enzyme is found in the cover of neurotropic bacteria and viruses, e.g. influenza, mumps or measles viruses, thus mimicking a brain infection. Three months after inducing neuroinflammation with NA to rats, an acute stressor was applied to investigate the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the stress response elicited, as well as the inflammatory activation of hypothalamic microglial cells. The acute stressor was forced swimming for 6 minutes. Afterwards, blood samples were retrieved to determine corticosterone levels by ELISA, and the brains extracted to analyze microglial cells in histological sections by immunohistochemistry with IBA1 and inflammatory markers by qPCR. Stressed rats previously injected with NA had increased levels of corticosterone compared with control rats that were equally stressed but had been ICV injected with saline. Also, qPCR studies in hypothalamic tissue revealed that NA-treated rats presented an increased expression of the genes for the inflammasome protein NLR family pyring domain containing 3 (NLRP3) and the microglial marker IBA1. Concomitantly, the morphological analysis of microglial cells located in the paraventricular nucleus (PVN) showed a morphological bias towards a slightly activated state in microglia of NA-injected rats compared to those of saline injected controls. These results suggest the long-term priming of hypothalamic microglial cells, and particularly those located in the PVN, after the acute ventricular inflammation induced by NA. Interestingly, increased corticosterone levels in NA-treated rats after exposure to an acute stressor point to an enhanced activation of the HPA axis. Thus, prior neuroinflammatory episodes, and in particular those associated to viral/bacterial infections, might result in subtle but persistent changes that condition the response to future challenges such as stressful events. Microglial cells could underlie those alterations.

Author Disclosure Information:

A. León-Rodríguez: None. **J.M. Grondona:** None. **M. Fernández-Arjona:** None. **C. Pedraza:** None. **M.D. López-Ávalos:** None.
Presentation Preference (Complete): Poster Only
Linking Group (Complete): None selected
Theme and Topic (Complete): C.07.f. Neuroinflammation - Microglia ; F.03.h. Stress-modulated pathways - Hypothalamus, amygdala, and bed nucleus
Nanosymposium Information (Complete):
Keyword (Complete): NEUROINFLAMMATION ; MICROGLIA ; STRESS
Support (Complete):
Support: Yes
Grant/Other Support: : Spanish Government: Ministerio de Economía, Industria y Competitividad Grant: SAF2017-83645
Grant/Other Support: : Spanish Government: Ministerio de Economía, Industria y Competitividad Grant: PID2020-117464RB-I00
Grant/Other Support: : Ministerio de Educación y Formación Profesional (Predoctoral Grant)
Grant/Other Support: : Plan Propio de Investigación y Transferencia de la Universidad de Málaga (Predoctoral Grant)

Special Requests (Incomplete):
Status: Incomplete