Social defeat stress induces microglial alterations and impaired cell survival in the hypothalamus according to behavioral phenotype

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Stress is the main environmental cause for depression, known to cause brain immune alterations. As major brain immune cells, microglia undergo transcriptional and, consequently, morphological changes that result in tissue damage, including new cell generation impairment. Even so, few brain regions have been thoroughly studied, excluding key regulators as the hypothalamus, in which this process remains partially unknown. Moreover, there is a poor understanding in physiology related to behavioral outcome. Therefore, it would be interesting to study the relationship between microglia and cell proliferation in stressed mice while controlling for behavior.

Here, we used the social defeat stress (SDS) paradigm as a depression-inducing protocol in 8-week-old male C57BL/6J mice for 10 consecutive days. Intruder mice behavior was analyzed to assess depression using behavioral tests and K-means clustering. By immunohistochemical and imaging procedures, microglial morphology, and distribution, as well as cell survival, were analyzed in the hypothalamic paraventricular, ventromedial and arcuate nucleus. Finally, statistical mediation analysis was conducted to evaluate the relationship among variables.

Results show mice response to SDS was different, being half the mice resilient and half sensitive to depressive-like symptoms. Microglial morphological activation was enhanced in the ventromedial and arcuate nucleus, especially in stress sensitive animals. Similar results were observed in cell survival, which was particularly affected in sensitive mice. Strikingly, these cell survival changes were statistically mediated by microglial activation.

As a conclusion, hypothalamic regions were found to respond differently to stress, accordingly to behavioral outcome, in terms of microglial activation and subsequent decrease in cell survival.

Acknowledgements

This study was supported by FEDER/Ministerio de Ciencia, Innovación y Universidades – Agencia Estatal de Investigación from Spain (PSI2017-83408-P to Pedraza C.), FEDER/Junta de Andalucía from Spain (UMA20-FEDERJA-112 to Pedraza C. and Pérez-

Martín M), and Ministerio de Educación, Cultura y Deporte from Spain (FPU19/03629 to Infantes-López MI and FPU16/05308 to Nieto-Quero A).