Plan Overview

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Title: The LPA1 receptor as a possible biomarker of vulnerability to depression. Role in microglial sensitization and neurogenic changes induced by juvenile stress. (DEPREPrimBRAIN)

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Project abstract:

Depression is a highly prevalent disease with devastating consequences, and depression diagnoses are increasing at an alarming rate, with a higher prevalence among females. Nevertheless, the underlying neurobiological mechanisms of mood disorders remain poorly understood.

Numerous studies have postulated that neuroinflammation mediated by microglia during sensitive periods of development contributes to the physiopathology of depression. The increase in inflammation can induce microglial priming that enhances susceptibility to secondary stress, which may trigger exaggerated inflammation. In addition, microglia are also an important regulator of hippocampal neurogenesis, which reduction have been linked to the neuropathology of stress-related mood disorders. When microglia are sensitized, the impact of stress on neurogenesis can be enhanced after a second inflammatory hit. Nevertheless, to date, studies aimed at determining the effects of stress on the interaction between microglia and neurogenesis have addressed the problem from very one-sided and unidirectional perspectives. Microglia are extremely sensitive to minor alterations in the central nervous system microenvironment, acting as sensors of local apoptotic and antineurogenic signals. Given that stress-induced apoptosis of newborn neurons is not unreasonable, we assume that neurogenic impairments may also contribute to microglial priming. However, despite the progress made, it is not currently known in detail how stress modulates microglial priming and neurogenic changes.

Identifying the biological factors that may be involved in microglial and neurogenic changes induced by stress early in development and that may increase the risk of developing mood disorders is essential for finding new potential therapeutic targets. The LPA1 receptor may be one such example.

Our group has identified the LPA1 receptor as a molecular factor that regulates neurogenesis in response to stress and is involved in mood regulation; dysfunction of LPA1 results in a phenotype of low resilience and is involved in the aetiology of depression. Moreover, microglial cells express LPA1 receptors; therefore, it would be reasonable to assume that LPA can play a role in the functional regulation of microglia. However, considerable heterogeneity has been observed in the microglial response to LPA, which acts as both a proinflammatory and anti-inflammatory molecule. This response may differ depending on the degree of

maturity and the activation status of microglia. For this reason, we propose to study for the first time the impact of stress during the sensitive period of development on adulthood vulnerability to depression, focusing on the bidirectional crosstalk between microglial priming and neurogenic dysfunction and the participation of LPA1 receptors in these processes. In addition, we propose to study whether the degree of expression of the LPA1 receptor is related to the risk of developing depressive symptoms after exposure to a second stressor so that it can be used as a possible biomarker of vulnerability to the development of depression. In addition, in animal models, increased vulnerability to the negative effects of stress and the development of depression has been observed in females, but the existence of sexual differences in the expression of LPA1 receptors has not been explored, therefore, will are to explore this possibility.

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The LPA1 receptor as a possible biomarker of vulnerability to depression. Role in microglial sensitization and neurogenic changes induced by juvenile stress. (DEPREPrimBRAIN)

Data Collection

What data will you collect or create?

The main objective of this project is to study (in animal models) the impact of stress during sensitive periods of development on vulnerability to depression in adulthood and the involvement of the microglial LPA1 receptor in this process. In addition, sex differences will be determined. Based on “two-hit” hypothesis, in mice, we will start with application of an intermittent juvenile stress and the application of a second acute stress in the adult period. the effects on depression and anxiety-like behaviours will be assessed. In addition, the response of microglia, neurogenic changes, and the expression of LPA1 receptors in microglia will be studied. The data collection will be generated from experimental protocol.The results obtained in the experiments will be plotted in Excel (Microsoft) software, images and videos will be stored in the cloud and on external hard disks.

How will the data be collected or created?

- Behavioural tests:

Hedonic behavioural data using the saccharin preference test, social behaviour in the social interaction test, recognition memory in the object recognition test and motivation and fatigability with the nest building test.

- Immunocytochemistry:

For neurogenesis and microglia studies (light microscopy and immunofluorescence).

- Cell quantifications:

Use of image analysis and stereology software.

- Molecular studies:

Determination of hippocampal cytokines (using luminex); study of hippocampal proteins using Quadrupole-Orbitrap Mass Spectrometry (Q-Orbitrap-MS) and western-blotting.

- Hormonal determinations in Plasma and serum:

Using a commercially available Enzyme Immunoassay Kit.

Documentation and Metadata

What documentation and metadata will accompany the data?

- Videos from animals’ behavioural tests.
- Microphotographs taken from immunohistochemistry and confocal studies. Scanned hippocampal images for microglia studies.
- Data from molecular analysis (proteomic) and gene expression of myelin genes, growth factors,

cytokines, endoplasmic reticulum stress and Unfolded protein response.
- All the data collected from behavioural analyses, immunocytochemical studies, cellular quantifications and molecular studies will be organised in Excel data sheets, separated in experimental groups (control; juvenile stress; adult stress and juvenile + adult stress) and organized by sex.
- Research data alongside files generated from analysis (SPPS / Excel) will be stored for 10 years from the completion date of the studies at the University of Malaga, within a password protected server (GoogleDrive) and y two separated external hard disk. Estimates that the volume of data will exceed TB.

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Ethics and Legal Compliance

How will you manage any ethical issues?

All procedures follow the current regulations on the use of animals in research and have been approved by the Ethics Committee of the University of Malaga (CEUMA 128/2021-A) and by the Directorate General for Agricultural and Livestock Production of the Andalusian Regional Government (25/01/2022/004). All persons involved in the project who will be working with research animals have the relevant accreditations to do so.

How will you manage copyright and Intellectual Property Rights (IPR) issues?

The data generated will be the property of the University of Malaga. The Agencia Estatal de Investigación, Ministerio de Ciencia e Innovación (SPAIN) and the project reference (PID2020-117464RB-I00) will be referenced in all works derived from the development of the project. The results susceptible of being patented will be protected. When results are published in scientific journals, they will be subject to licensing or editorial policy restrictions.

Data sharing will require the data use agreement from the Principal Investigators (Dr. Carmen Pedraza, mdpedraza@uma.es; Dr. Margarita Pérez (marper@uma.es) and the investigators who have participated in the collection and/or processing of the data concerned.

Storage and Backup

How will the data be stored and backed up during the research?

All data will be stored in the cloud (Google Drive). Simultaneously a backup of the data will be stored in two hard drives kept in different (guarded by the two principal investigators of the project)

How will you manage access and security?

The access to the cloud data depends on sharing authorization and password, which will be available only to authorized people with research purposes only.

Selection and Preservation

Which data are of long-term value and should be retained, shared, and/or preserved?

All the research data will be kept for 10 years in our servers and in the cloud (GoogleDrive).

What is the long-term preservation plan for the dataset?

All the research data will be kept for 10 years.

Data Sharing

How will you share the data?

All data resulting from the development of this project will be available in scientific communications presented at conferences and in manuscripts that will be published in peer-reviewed scientific journals. As far as possible, they will be open access or, once the data have been presented, they will be made available to the public through the institutional repository (RIUMA). In addition, they will be disseminated to society through the participation of research and work teams in science dissemination activities.

Are any restrictions on data sharing required?

The use of the data may only be used for scientific purposes or for the dissemination of science.

Responsibilities and Resources

Who will be responsible for data management?

The project coordinators (Carmen Pedraza and Margarita Pérez-Martín)

What resources will you require to deliver your plan?

The IT services and general library of the University of Malaga currently have all the necessary resources to meet the requirements of this research data management plan.