Microglia Cell Signaling in Models of Parkinson's Disease

LSU Health NEW ORLEANS School of Medicine

Alexandra Minnard, Hailie Goldthorpe, Tendayi Mpofu, Sayantani Bhattacharjee, Jorgelina Calandria, PhD

Louisiana State University Health Sciences Center, Neuroscience Center of Excellence

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects the dopaminergic neurons in the substantia nigra in elderly population(1). Microglia, the resident macrophage-like cells located in the central nervous system, mediates synaptic pruning, perform phagocytosis of cellular depositions and waste, and release pro and anti-inflammatory responses contributing to neurodegeneration or neuroprotection (2). Microglia polarizes into different M1 and M2 phenotypes. These phenotypes modulate defensive or neuroprotective efforts to modulate neuroinflammation. The M1 phenotype exhibits pro-inflammatory cytokine responses, while the M2 phenotype demonstrates anti-inflammatory responses with high LC3-associated phagocytosis (LAP) that scavenges debris and unfolded fibrillar subproducts like alpha-synuclein fibrils (3).

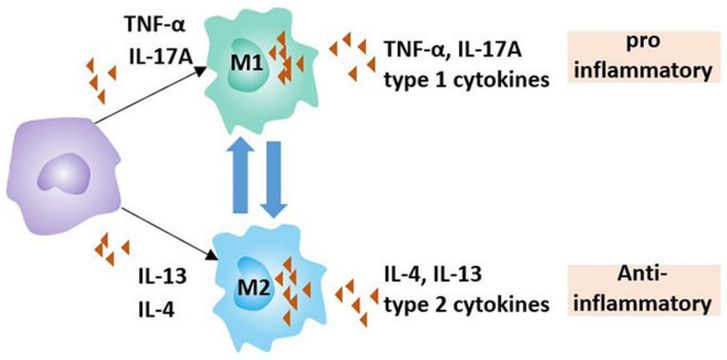
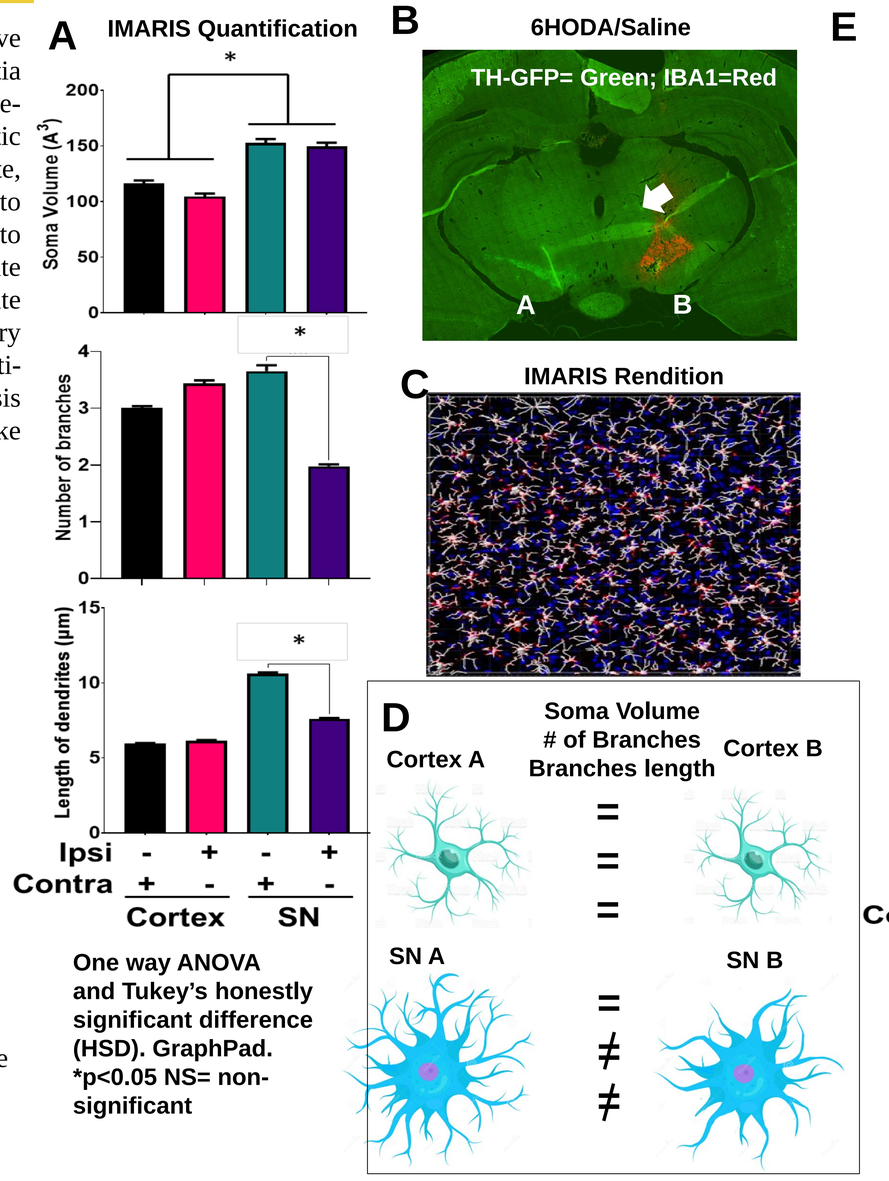


Figure 1. Dopaminergic neurons carrying mutated Alpha-synuclein releases stress signals that activates astrocytes and microglia. The accumulation of α-syn leads to oxidative stress and proinflammatory responses in which microglia is polarized to M1 phenotype. M1 microglia secrete inflammatory responses such as TNF-α which is a pro-inflammatory cytokine. M2 microglia secrete inflammatory responses such as IL-4 which is an anti-inflammatory cytokine.

Our **overall hypothesis** is that DHA derivative, Maresin 1, induce the second step in the polarization from M1 to M2, leading to a decrease in the inflammatory signals and increasing the LAP activity of microglial cells.

Results



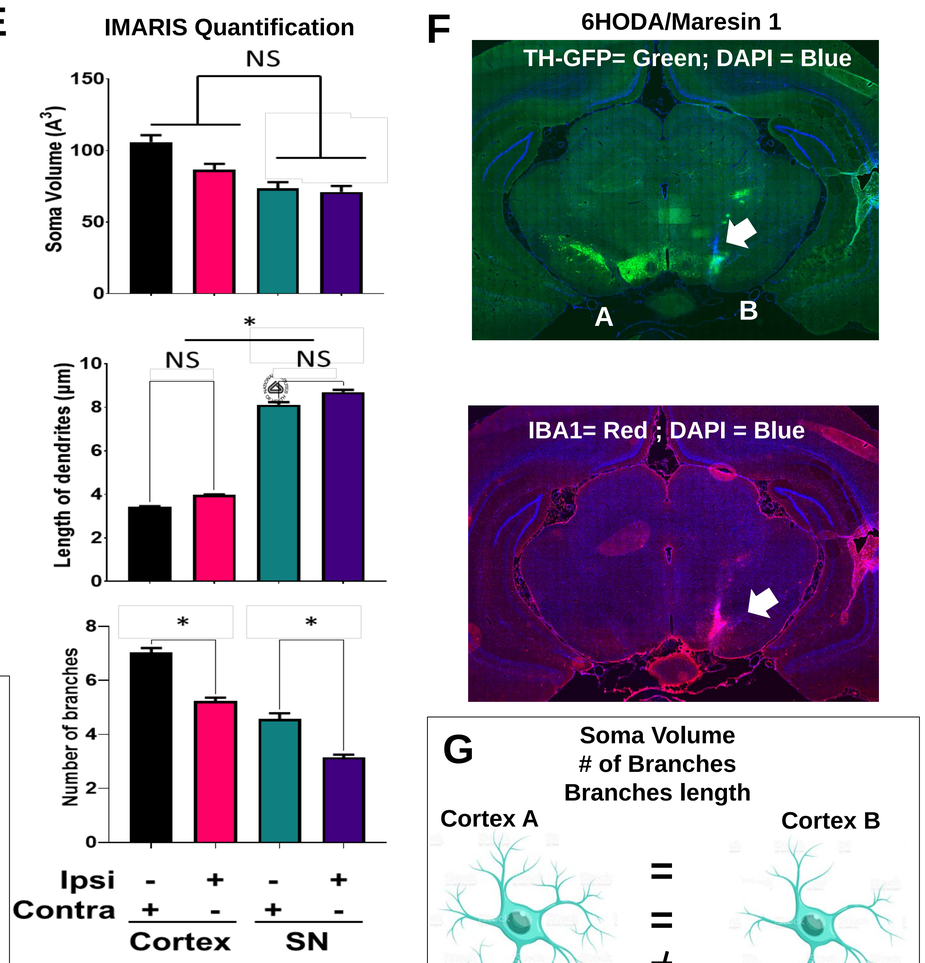
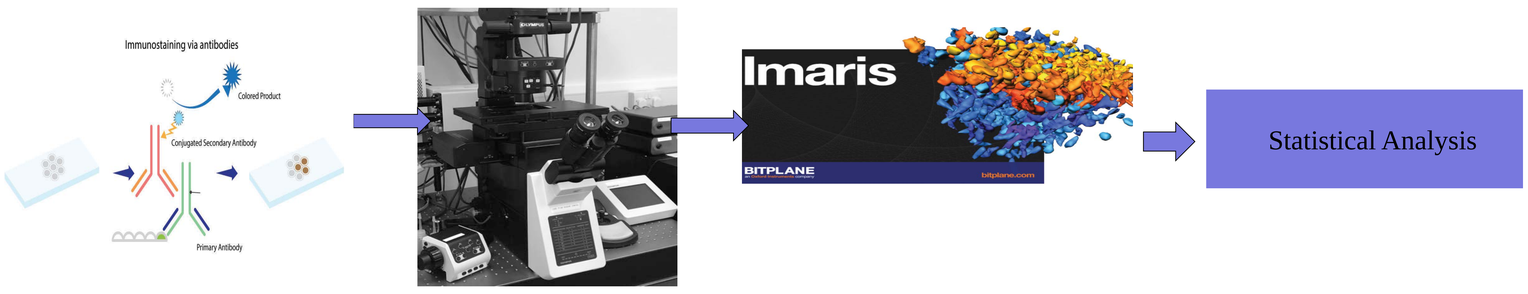


Figure 2. Cortex and Sustantia nigra (SN) microglia from the treated 6-hydroxydopamine rat were imaged and analyzed **A.** Statistical analysis of soma volume, statistical analysis of number of branches and statistical analysis of length of dendrites in cortex and SN microglia treated with saline control **B.** Stereotaxic rendering of rat brain and point of injection **C**. Imaris rendering of microglia **D**. Renderings of side A and B cortex and SN microglia (saline control) **E.** Statistical analysis of soma volume, statistical analysis of length of dendrites, and statistical analysis of number of branches in cortex and SN microglia treated with Maresin 1 **F.** Stereotaxic rendering of Maresin treated rat brain and point of injection **G.** Renderings of side A and B cortex and SN microglia

Methods

This hypothesis was tested "*in vivo*" in a 6- hydroxydopamine (6-HODA) toxicity rat model and "*in vitro*", in adult rat brain cultures of microglial cells treated with TNF-alpha, C1q and IL-alpha or alpha-synuclein fibrils to induce M1 polarization.



Immunocytochemistry was used to detect p65 nuclear translocation and LC3 decorated vesicles, and immunohistochemistry using IBA1 was used to detect microglial cells in different areas of the rat brain. Images were taken using a FluoView 1200 confocal microscope. The confocal capture z-stacks were processed using Imaris 9.7 and the data was statistically analyzed.

Conclusion

- In the 6HODA toxicity model, microglia were more abundant, and the shape resembles the M2 phenotype more in the rats treated with Maresin 1 than in the saline control.
- In culture, ELV34 and Maresin 1 induced a decreased in p65 translocation, however Maresin was more effective in eliciting LC3-phagocytosis.
- Maresin 1 induced significant positive effects in the polarization from M1, inflammatory to M2, pro-survival phenotype laying the road for a future therapeutical development

References

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