Sartori *et al.*: *Intrinsic Activity*, 2023; **11**(Suppl.1):A2.12
doi:10.25006/IA.11.S1-A2.12
published online: 22 September 2023

INTRINSIC ACTIVITY

27th Scientific Symposium of the Austrian Pharmacological Society

Vienna, 29–30 September 2023

MEETING ABSTRACT

A2.12

Microglia profiling in a model of high trait anxiety

Simone B. SARTORI[1], Mohammad EBRAHIMI DARAN[1], Michael LANGESLAG[2], Maria KHARITONOVA[1], Bilge UGURSU[3,4], Susanne A. WOLF[3,4], Anupam SAH[1], Nicolas SINGEWALD[1,*]

[1]Department of Pharmacology and Toxicology, Institute of Pharmacy and Center for Molecular Biosciences Innsbruck (CMBI), University of Innsbruck, Austria; [2]Department of Pharmaceutical Chemistry, Institute of Pharmacy, University of Innsbruck, Austria; [3]Department of Ophthalmology, Charité University Hospital, Berlin, Germany; [4]Department of Psychoneuroimmunology, Max Delbrück Center for Molecular Medicine in the Helmholtz Society, Berlin, Germany

Background: Neuroinflammation with altered microglial function is proposed to contribute to the pathology and outcome of anxiety disorders in specific patient subgroups. We have previously shown that a mouse model of high trait anxiety (HAB) displays increased microglial density in key regions of anxiety circuits, including the hippocampus, compared to normal-anxiety (NAB) controls. Microglia, however, can transit from a neuroprotective to a pro-inflammatory state. These functions of microglia are tightly linked with their intricate shape. In order to get insight into the functional states of increased microglia densities in anxiety-prone subjects, we investigated morphological and genetic characteristics of microglia in HAB *vs.* NAB mice.

Methods: Anxiety-related behaviours of HAB and NAB mice were assessed in the light/dark test. Microglia were visualized by using immunohistochemistry for ionized calcium-binding adapter molecule 1 (Iba1). Microglial morphology was assessed using the MICMAC automated analysis aided with MATLAB programing. Gene profiling was performed by single-cell RNA sequencing of FACS-sorted whole brain microglia.

Results: Using the automatized MICMAC analysis we now replicated the observed increased microglial density in the hippocampus, previously assessed using manual counting. Additionally, we observed that the prevalence of amoeboid, 'activated' microglial morphology was significantly higher in HAB as compared with AB. The expression of phagocytic cell surface markers including CX3CR1, CR3, and TREM2 was also altered in HAB as compared to NAB mice of both sexes. Interestingly, sex differences in pathways of microglial expression, microglial morphology as well as synaptic pruning were revealed in the brain of HABs as compared to NABs. Finally, we demonstrate that reducing microglia activation either systemically or locally in the hippocampus by administration of the anti-inflammatory drug minocycline attenuated the enhanced anxiety in HABs.

Discussion: The increased abundance of amoeboid microglia together with the altered expression of the cell surface markers CX3CR1, CR3, and TREM2 in HABs may be indicative of enhanced phagocytosis, activation and/or altered tissue integrity in the hippocampus of HABs. These changes in the hippocampal microenvironment are suggested to contribute to the neuronal dysfunctions and altered neurogenesis previously reported in HABs and putatively supporting their anxious phenotype. Furthermore, we provide proof of concept that reducing microglia activation in the hippocampus is paralleled by attenuation of the high anxiety in HABs. Thus, the activated microglia system could represent an interesting pharmacological target for the therapy of hyperanxious individuals with an altered neuroinflammatory system.

Acknowledgements: Supported by the Austrian Science Fund FWF (grant no. I3875) and the German Research Foundation DFG (grant WO-1418/6-1).

Keywords: anxiety – microglia – phagocytosis – neuroinflammation

*Corresponding author e-mail: *nicolas.singewald@uibk.ac.at*