Consequences of Microglial-Mediated Recruitment of Inflammatory Monocytes to the Brain with Psychological Stress

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Psychological stress contributes to the development of anxiety and depression. Recent clinical studies have reported increased inflammatory leukocytes in circulation of individuals with stress-related psychiatric disorders. Parallel to this, our work in mice shows that stress causes release of inflammatory monocytes into circulation. In addition, stress caused the development of prolonged anxiety that was dependent on inflammatory monocytes in the brain. Therefore, we hypothesize that chronic stress drives the production of inflammatory monocytes that are actively recruited to the brain by microglia, and these monocytes augment neuroinflammatory signaling and prolong anxiety. Here we show that repeated social defeat (RSD) in mice activated threat appraisal centers in the brain that spatially coincided with microglial activation and endothelial facilitation of monocyte recruitment. Moreover, microglial depletion with a CSF1R antagonist prior to stress prevented the recruitment of monocytes to the brain and abrogated the development of anxiety. Cell-specific transcriptional profiling revealed unique mRNA signatures of monocytes in the blood, monocytes in the brain and microglia in the brain after RSD. For example, microglia selectively enhanced the expression of key chemokines, while monocytes highly expressed IL-1 β , MMP9 and Ly6C. Consistent with these profiles, the recruited inflammatory monocytes with stress adhered to IL-1R1+ neurovascular endothelial cells and this interaction was blocked by microglial depletion. Furthermore, disruption of IL-1 β signaling by caspase-1^{KO} specifically within bone marrow-derived cells revealed that monocytes promoted angiogenesis through stimulation of neurovascular IL-1R1 by IL-1 β . Collectively, the development of anxiety during stress was caused by microglial recruitment of IL-1 β -producing monocytes that stimulated brain endothelial IL-1R1. Thus, monocyte IL-1 β production represents a novel mechanism that underlies behavioral complications associated with stress-related psychiatric disorders.