Long COVID in K18-hACE2 mice causes persistent brain inflammation and neurocognitive impairment

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Growing evidence suggests cognitive abnormalities exist in patients suffering from long COVID. Because clinical data on long COVID patients are mostly from associational studies and complicated by confounding variables, it is critical to define specific mechanisms responsible for long-term consequences on the brain in an animal model of long COVID. In this study, using a low dose of SARS-CoV-2 infection in K18-hACE2 mice to elicit mild disease, we developed a mouse model of long COVID. In mice 45 days following recovered from SARS-CoV-2 infection, protein expression determined by immunofluorescence staining revealed a significant increase in expression of the pro-inflammatory kinin B1 receptor, and the inflammatory cytokines, IL-6 and TNF-alpha, in the brain regions relevant to neurocognitive function (hippocampus, amygdala, and prefrontal cortex). Furthermore, a significant increase in B1R expression and fibrosis was found in the lungs. In behavioral tests, mice recovered from a mild SARS-CoV-2 infection spent less time in the open portion of the zero maze, a measure of elevated anxiety, and entered fewer arms in the Y maze, an indication of reduced exploration. These data demonstrate a persistent effect of SARS-CoV-2 on the brain and lungs, and that the B1R could represent an important pathway to drive inflammation. Infection of K18-hACE2 mice with sub-lethal doses of SARS-CoV-2 reproduce important aspects of long COVID. Because inflammation and B1R expression has been implicated in neurodegenerative disease such as Alzheimer's disease and dementia, the persistent effects after recovery from SARS-CoV-2 could increase future risk of these diseases.