Bradykinin Receptor Serves as a Target for Reducing Lung Fibrosis in COVID Mouse Model

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INTRODUCTION

Evidence suggests that primary consequences of COVID-19 are pulmonary inflammatory responses, including cytokine and bradykinin storms. Elevated bradykinin, an inflammatory mediator for being a source of bronchoconstriction and physiological pulmonary complications, has been reported in severe COVID-19 cases. Reduced lung function has also been reported in patients recovered from COVID-19, including mild disease. In a mouse model of long COVID-19, we found evidence of elevated fibrosis in the lungs, as well as elevated expression of the bradykinin 1 receptor (B1R) that correlated with fibrosis (1). While evidence displays the pulmonary complications associated with recovery from COVID-19, no studies have tested potential therapeutic targets to prevent this pulmonary damage.

MATERIALS & METHODS

K18-hACE2 mice were implanted with an osmotic minipump to continually deliver the B1R antagonist SSR240612 at 10 mg/kg/day or vehicle (40% DMSO, 60% NaCl) at a rate of 0.11 µl/hr, 5 weeks). We administered a low dose of SARS-CoV-2 (4000 TCID50) to elicit mild to moderate disease or sham infection intranasally to K18-hACE2 mice and K18-hACE2 B1R antagonist mice. Mice were sacrificed 30 days post infection and lungs were assessed based on visual assessment, Masson's trichrome (used to label collagen associated lung fibrosis), and B1R immunohistochemistry.

RESULTS

Our preliminary data suggests that administering a B1R antagonist could reduce fibrosis of the lungs following COVID-19. Other additional findings indicate a potential reduction in neuro-inflammatory response.
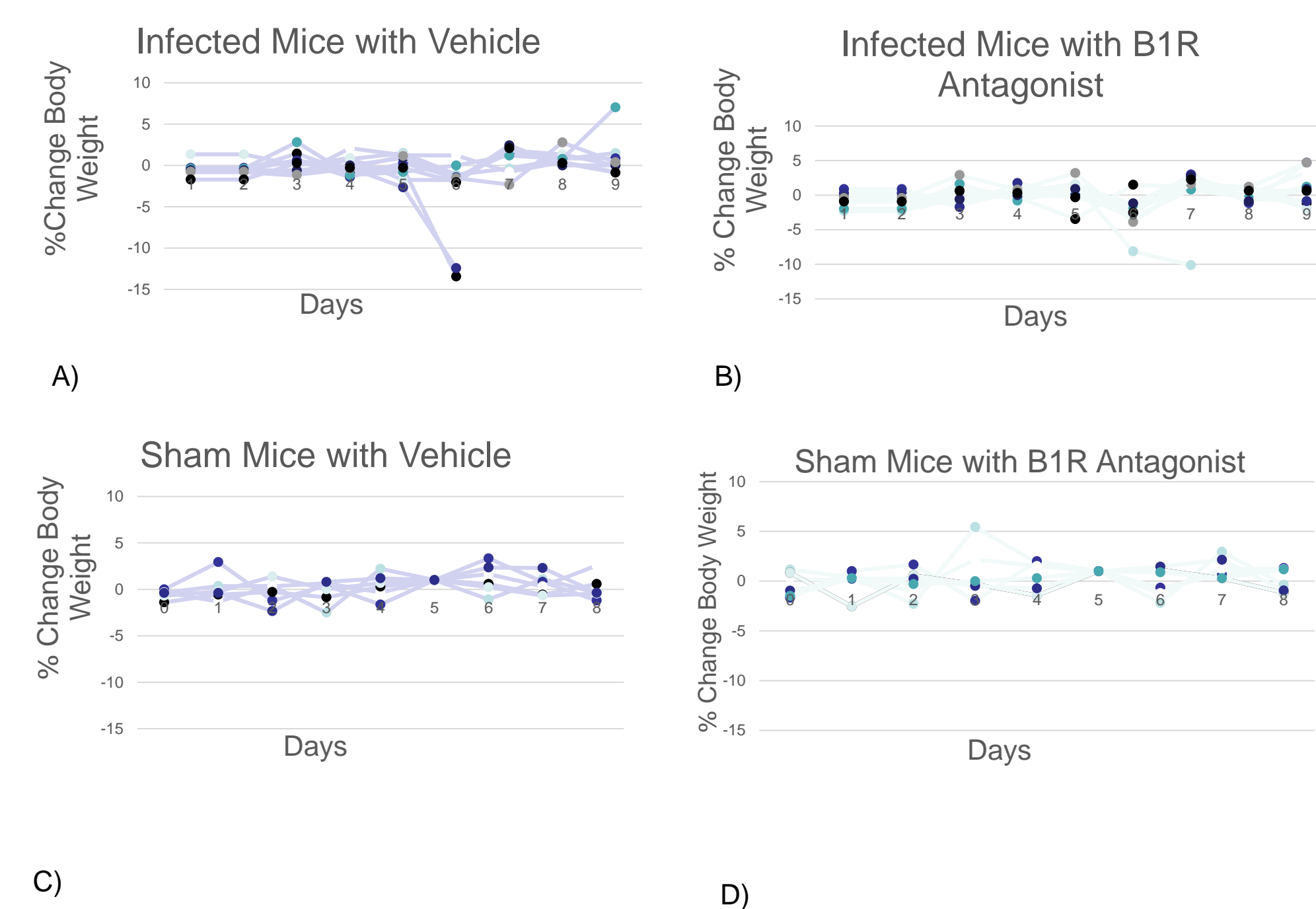

Figure 1. Mice were weighed daily following SARS-CoV-2 infection or Sham procedure. Mice that developed severe COVID-19 (2 Vehicle treated and 1 B1R antagonist treated) rapidly lost weight and were euthanized. Analysis of percentage change in body weight between B1R antagonist vs vehicle in both the COVID infected mice (Figure 1a/b) and the sham infected mice (Figure 1c/d) are insignificant.
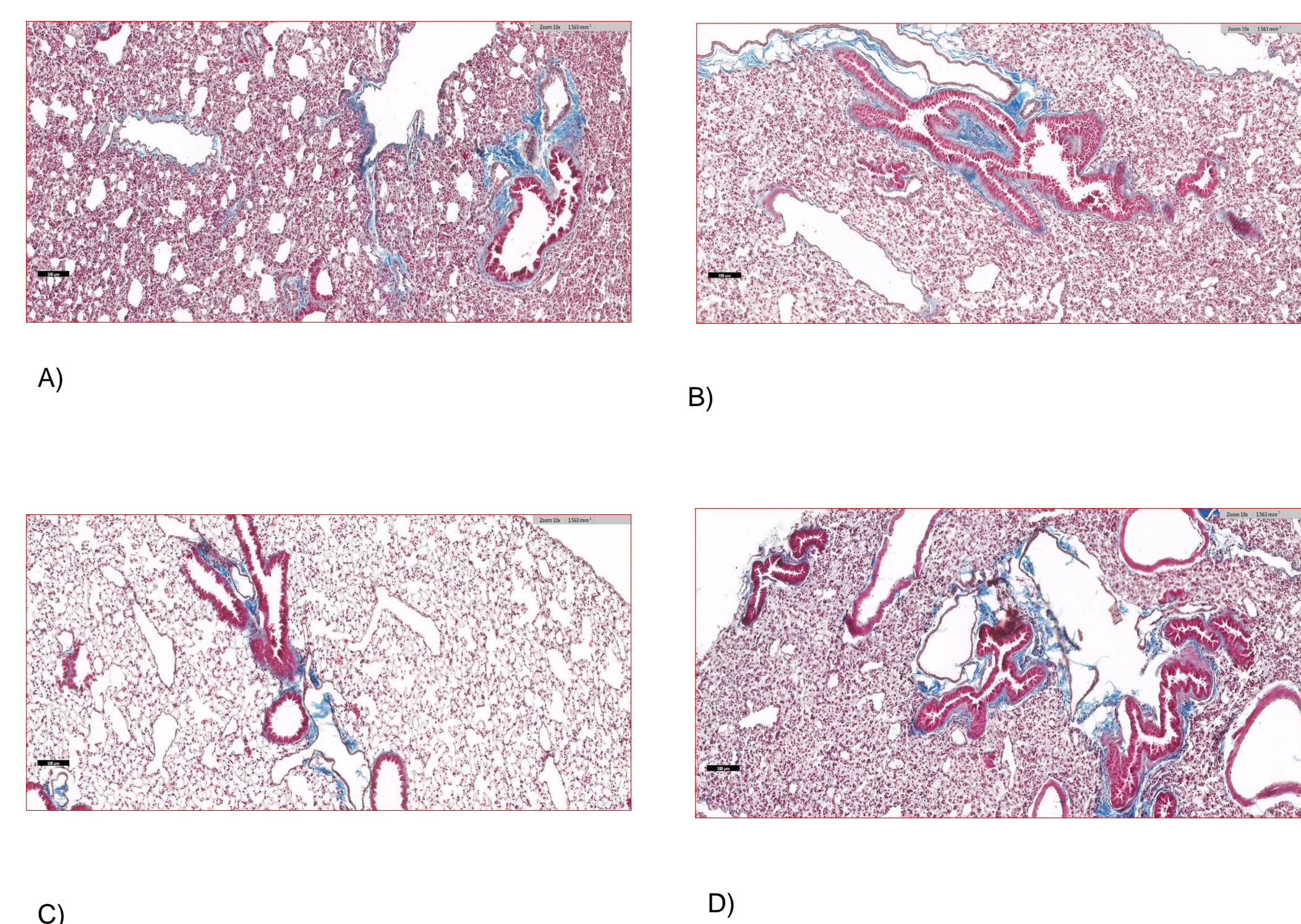

Figure 2. Masson's Trichrome staining in COVID infected mice with B1R antagonist (Figure 2a) appear to show reduced collagen and fibrosis compared to COVID infected mice with vehicle (Figure 2b). Sham infection for both B1R antagonist (Figure 2c) and vehicle (Figure 2d) appear to display reduced collagen and fibrosis than infected mice.

Figure 3. Quantification using Image J found a significant reduction collagen and fibrosis in the SARS-CoV-2 infected mice treated with the B1R antagonist.
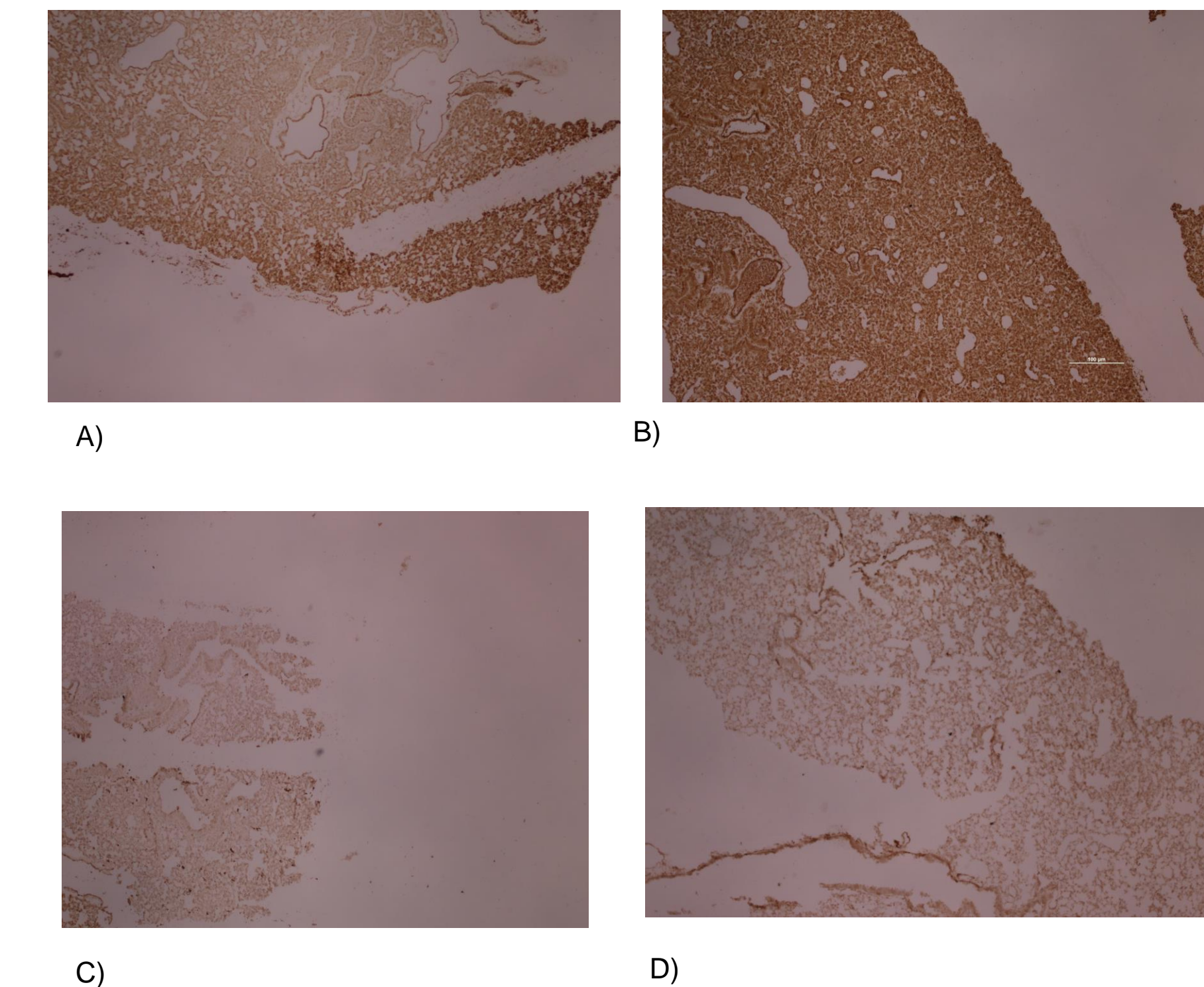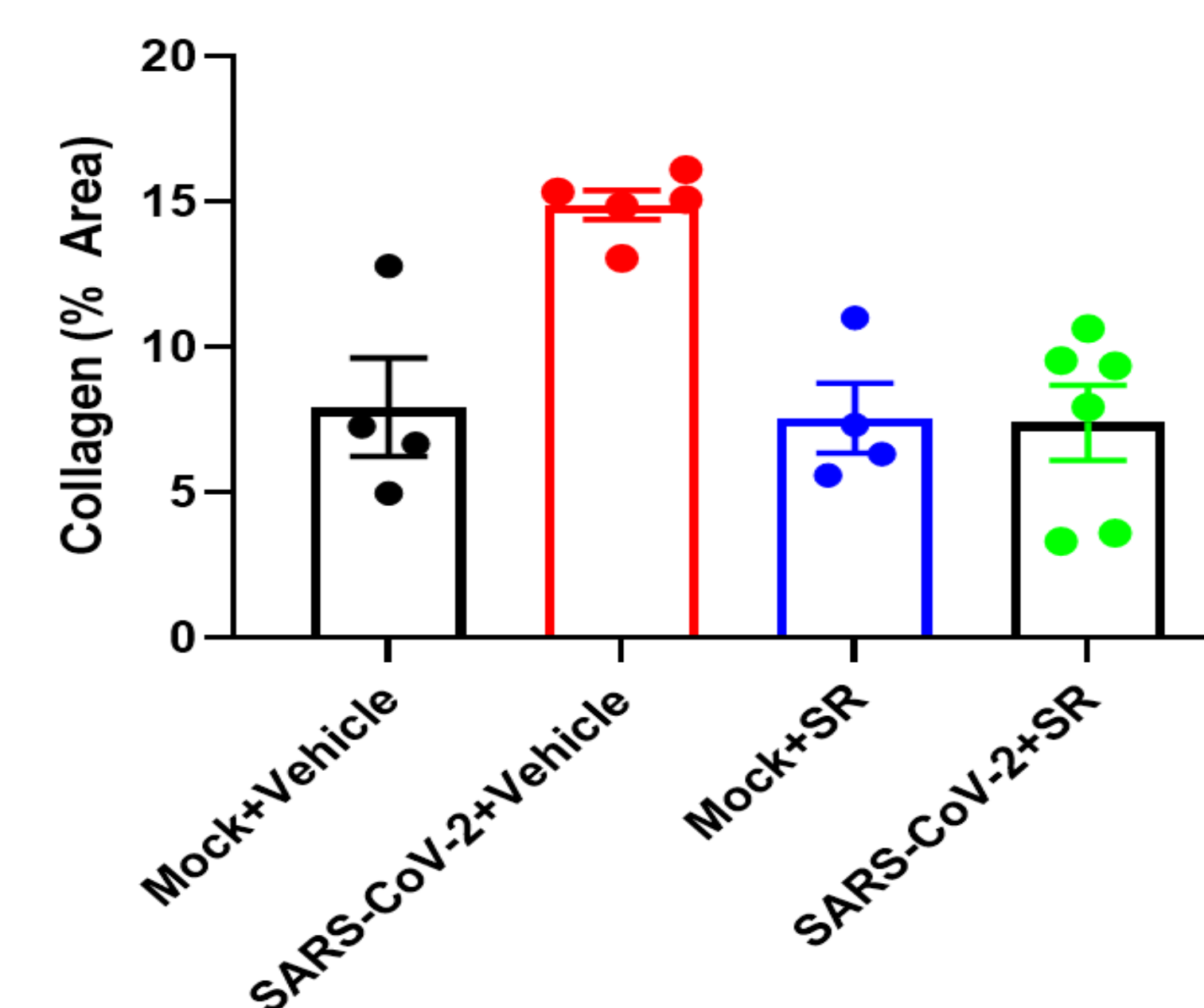

Figure 4. Immunohistochemistry of B1R indicates that B1R is upregulated during infection, such that the infected mice (Figure 4a/b) have more B1R than the sham treated (Figure 4c/d) mice. This expression is attenuated by the B1R antagonist (Figure 4a).

DISCUSSION

These data suggest that B1R could represent an important therapeutic target to reducing the degenerative effects of inflammation from COVID. Future studies will continue to evaluate the neurocognitive effects of B1R antagonism in COVID models.

REFERENCES

References: (1) Srinivas Sriramula, Rohan Parekh, Drew Theobald et al. Long COVID in K18-hACE2 mice causes persistent brain inflammation and cognitive impairment, 06 July 2022, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-1818930/v1]

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