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IDWeek, October 21–24, 2026
Washington, DC, USA

Ensitrelvir Suppresses Fatigue-like Symptoms Derived from SARS-CoV-2 Infection in Hamsters

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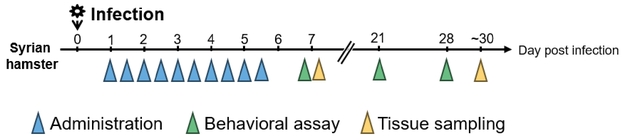
Background and Purpose

Post-COVID-19 condition, or long COVID, is characterized by persistent symptoms following SARS-CoV-2 infection, and fatigue is among its most prevalent and debilitating manifestations. Chronic inflammation and mitochondrial dysfunction have been proposed as potential contributors, but treatment options remain limited. In a hamster model, ensitrelvir (ENS), an oral SARS-CoV-2 3CL protease inhibitor, was previously shown to attenuate prolonged olfactory abnormalities following infection [1]. This study characterized persistent alterations in motor performance and skeletal muscle function after SARS-CoV-2 infection and evaluated whether early ENS treatment attenuated these effects.

Methods

Male Syrian hamsters were intranasally inoculated 10,000 $TCID_{50}$ of with the SARS-CoV-2 Delta variant. ENS was orally administered twice daily for 5 days starting 24 h after infection at a dose regimen designed to achieve clinically relevant human exposure. Fatigue-like manifestations were assessed by open-field activity at 1 week, grip strength at 1, 3, and 4 weeks, treadmill performance at 3-4 weeks [2], and ex vivo soleus muscle contractile force at 4 weeks post-infection. Skeletal muscle transcriptomic analysis was performed at 1 and 4 weeks to investigate pathways related to mitochondrial function, energy metabolism, and inflammation. Results were compared among non-infected, infected vehicle-treated, and ENS-treated animals.

Figure 1 Detailed overview of the study design



Acknowledgement

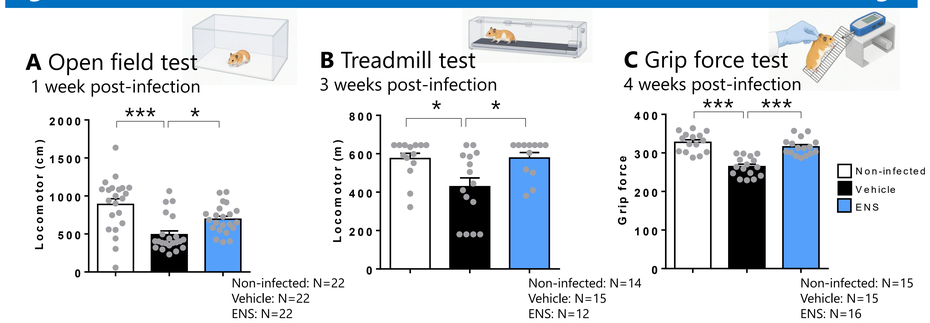
SARS-CoV-2 strain was kindly gifts from National Institute of Infectious Diseases (Japan). This study was funded by Shionogi & Co., Ltd.

References

[1] Tashima R et al. *Antiviral Res. 2025 Nov:243:106270.*
[2] Castro B et al. *Bio Protoc. 2017 Apr 20;7(8):e2237.*

Results

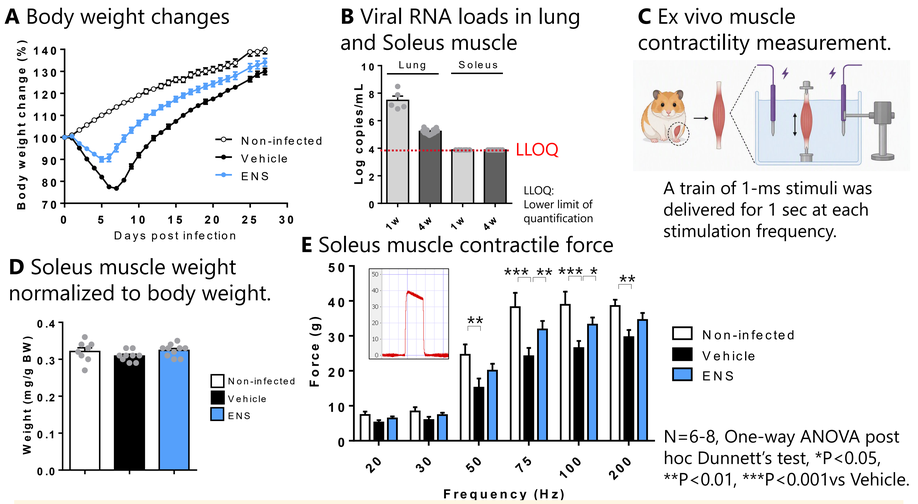
Figure 2 Behavioral Assessment of Motor Performance and Muscle Strength



The hamsters were assigned into the following three groups: ENS (infected and received ENS), vehicle (infected but received vehicle only), and non-infected (non-infected and received vehicle only) groups. One-way ANOVA post hoc Dunnett's test, *P<0.05, ***P<0.001 vs Vehicle.

Early ENS treatment attenuated SARS-CoV-2-associated reductions in open-field activity, treadmill performance, and grip strength at the time points shown.

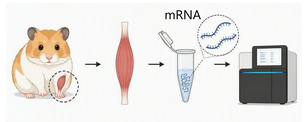
Figure 3 Effects of ENS on soleus muscle outcomes following SARS-CoV-2 infection.



Early ENS treatment attenuated the SARS-CoV-2-associated reduction in soleus muscle contractile force without a detectable effect on soleus muscle mass.

Figure 4 RNA-seq analysis of the soleus muscle after SARS-CoV-2 infection

A Experimental workflow for soleus muscle RNA-seq analysis



Volcano plots showing differentially expressed genes between groups in the soleus muscle at 1 and 4 weeks post-infection. Significant upregulated and downregulated genes are highlighted in red and blue, respectively.

ENS preserves mitochondrial transcriptional programs and suppresses inflammatory signaling in soleus muscle after SARS-CoV-2 infection.

B Effects of SARS-CoV-2 infection and ENS treatment on skeletal muscle gene expression.

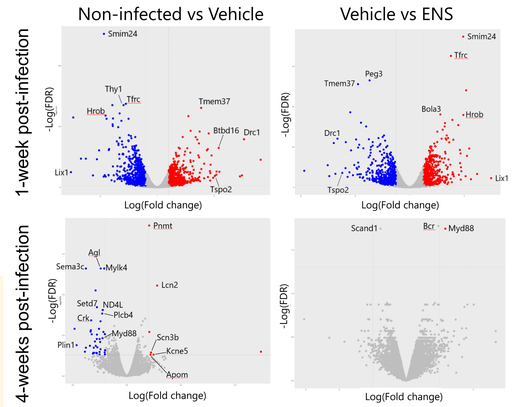


Table 1. RNA-seq–based analysis of mitochondrial complex gene expression at week 1 post-infection

Mitochondria complex		Example gene	1-week post-infection	
			Vehicle	ENS
Complex I	Core	Nd1-6, Ndufs1-3,7,8	↓	↑
	Supplementary	Ndufa1-13, Ndufb2-11, Ndufc1,2, Ndufs4-6	↓	↑
Complex II	Core	Sdha-d	↓	↑
Complex III	Core	Cyb, Cyc1, Uqcrfs1	→	→
Complex IV	Core	Co1-3	→	→
Complex V	Core	Atp5a1, Atp5c1, Atp5e, Atp5f1, Atp5g1-3	→	→

Vehicle indicates changes relative to the non-infected group, whereas ENS indicates changes relative to the vehicle-treated group. Arrows denote the direction of change: upward arrows (↑) indicate increased expression, downward arrows (↓) indicate decreased expression, and horizontal lines (→) indicate no change in expression.

Conclusion

SARS-CoV-2 infection induced persistent deficits in motor performance and soleus muscle function despite the absence of detectable infectious virus in the muscle. Muscle weight was unchanged, suggesting qualitative muscle dysfunction. Transcriptomic analysis revealed early suppression of mitochondrial electron transport chain genes and later induction of inflammatory genes, both attenuated by early ENS treatment. These findings suggest that early ENS treatment attenuates prolonged fatigue-like sequelae, potentially by mitigating mitochondrial dysfunction and inflammation.