Neuroprotective potential of the MasR agonist in the experimental intracerebral haemorrhage

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Background

Intracerebral haemorrhage (ICH) is the second most common stroke. Even though there has been an encouraging trend in ICH survival during recent years, the rate of disability has not reduced due to post-ICH brain damage, which still lacks effective treatments. Systolic blood pressure is recommended to be acutely decreased and maintained to lower than 140mmHg after ICH.[1] ACE2/Angiotensin 1-7/MasR is a regulatory axis of the renin-angiotensin system reducing blood pressure. Recent studies reported that it exerts neuroprotective effects and enhances functional recovery in some neurological diseases, such as traumatic brain injury and ischemic stroke.[2] However, its non-blood pressure-related roles in ICH have not been studied. This study aimed to investigate the neuroprotective effects of the MasR agonist (AVE0991) in the experimental ICH.

Methods & Results

Experimental ICH:
- Hemin-induced *in vitro* model
- Collagenase intrastriatal injection-induced *in vivo* model

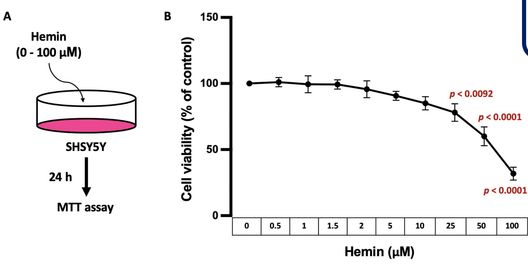


Figure 1. Hemin-induced ICH model *in vitro*. ***A)*** Experimental outline. ***B)*** Cell viability. Viabilities of SHSY5Y cells significantly reduced after incubated with hemin at 25 μM, 50 μM and 100 μM for 24 h. 100 μM hemin was chosen to induce the *in vitro* ICH model in this study.

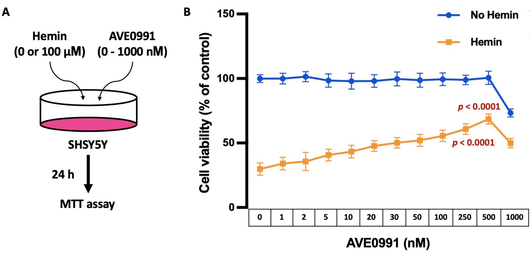
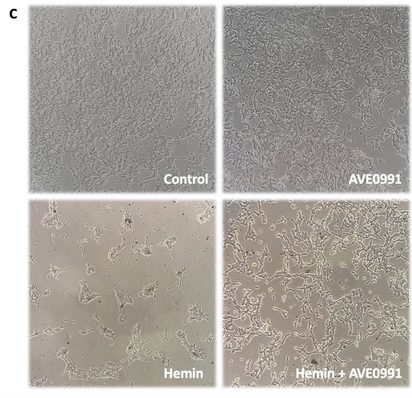


Figure 2. ***A)*** Experimental outline. ***B)*** AVE0991 protected SHSY5Y cells from hemin-induced cell death in a concentration-dependent manner. ***C)*** Representative images of SHSY5Y 24 h after incubated with 1% DMSO (Control), AVE0991 (500 nM), hemin (100 μM) and hemin (100 μM) + AVE0991 (500 nM).



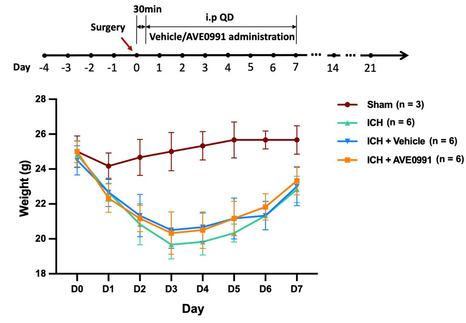


Figure 3. There was no significant change in the mouse weight after drug administration.

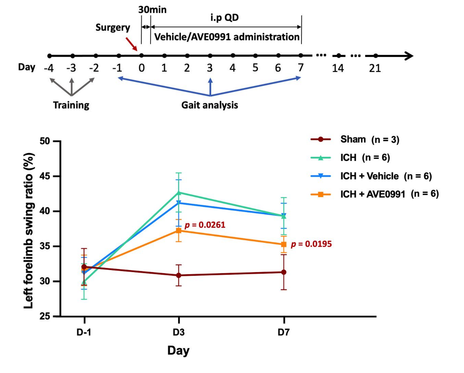


Figure 4. AVE0991 administration significantly decreased the swing ratio of the affected forelimb.

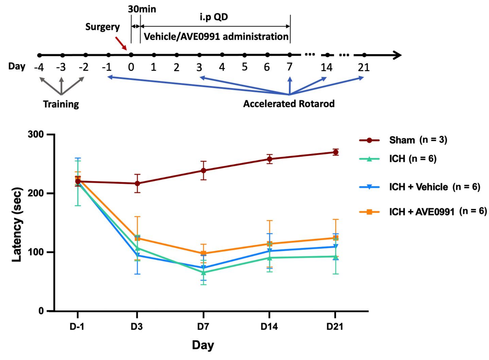


Figure 5. There was a nonsignificant trend that administrating AVE0991 after ICH increases latency to fall.

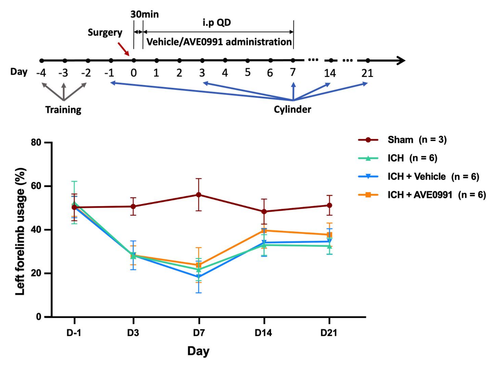


Figure 6. AVE0991 showed a nonsignificant trend in increasing the usage of the affected forepaw after ICH.

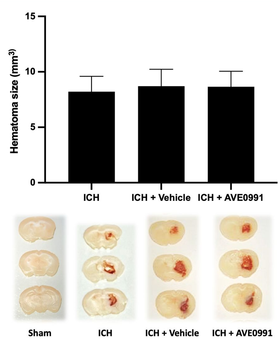


Figure 7. The AVE0991 dosage used in this study did not significantly change the haematoma sizes at day 1.

Discussion & Conclusions

The results of this study present a trend but not a significant trend that AVE0991 improves motor coordination and locomotor ability after ICH *in vivo*. However, AVE0991 reduced hemin-induced neuronal death *in vitro*, and AVE0991 with a dosage not affecting haematoma size alleviated gait abnormality significantly *in vivo*, indicating that AVE0991 tends to show neuroprotective effects in experimental ICH. The neuroprotective potential of AVE0991 still needs further investigations, such as neuronal histological changes and blood pressure alterations after administration and relevant neuroprotective mechanisms.

References:

1. Rabinstein, A.A. (2018). DOI: 10.1161/STROKEAHA.117.020058.
2. Janatpour, *et al.* (2019). DOI: 10.1089/neu.2019.6376.