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T-705 as a Potential Therapeutic Agent for Rabies

TO THE EDITOR—Rabies is a lethal zoonotic disease caused by rabies virus (RABV), a nonsegmented, negative-sense, single-stranded RNA virus. It enters the host via a bite site and travels in a retrograde fashion to the central nervous system (CNS), where it multiplies and centrifugally spreads to other organs. The almost 100% fatality rate is due to viral evasive strategies and an intact blood-brain barrier, which does not allow immune effectors into the infected brain [1].

Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide), also known as "T-705," has been studied for its antiviral properties against many RNA viruses, both in vitro and in vivo, such as influenza virus, West Nile virus, and Ebola virus [2, 3]. Recently, Yamada et al reported using T-705 in mouse model as an alternative to rabies immunoglobulin in rabies postexposure prophylaxis [4]. RABV multiplication in neuro-2a cells was efficiently suppressed in the presence of T-705. The improved survival rate was best shown in mice inoculated intramuscularly with RABV and administered T-705 (300 mg/kg/day orally) daily for 7 days starting 1 hour after inoculation.

We also evaluated the effect of T-705 in rabies infection. Neuro-2a cells were inoculated with RABV CVS-11 at different concentrations (1, 5, 25, or 125 50% tissue culture infective doses [$TCID_{50}$]/mL) for 1 hour, and medium was replaced with medium containing T-705 at a concentration of 0, 200, 400, or 800 μM. After 24 and 48 hours, the cells were stained with fluorescein isothiocyanate–conjugated anti-RABV monoclonal globulin and underwent immunofluorescence for detection of RABV antigens. The largest reductions in the RABV load and number of foci were found in cells treated with T-705 at a concentration of 800 μM. The results were in accordance with those of Yamada et al in terms of amount of viral RNA in the cells and supernatant fluid collected 48 hours after infection and measured by real-time polymerase chain reaction analysis. Thus, our in vitro results confirm that T-705 has the ability to suppress RABV multiplication.

Next, we evaluated whether T-705 could be used as therapeutic agent in RABV-infected mice. The prior study demonstrated T-705 as a promising agent for postexposure prophylaxis. Here, we inoculated mice intracerebrally with CVS-11 at 25 $TCID_{50}$/mL to represent the stage of infection when RABV has already been transported from the entry site to the CNS. T-705 was dissolved in 0.4% carboxymethyl cellulose and orally administrated to the infected mice at a dosage of 50 mg/kg/day, twice daily for 6 days, starting 4 hours after inoculation. The disease progression was monitored daily for 21 days.

The control mice, infected with CVS-11 without T-705 administration, died 8–10 days after inoculation. All but 1 RABV-infected mouse receiving T-705 died 6–10 days after inoculation (Figure 1). The surviving mouse did not exhibit any symptoms and has remained healthy until the time of writing (6 months after inoculation).

Comparison of the time taken to develop sickness between RABV-infected mice that did and those that did not receive T-705 was not significantly different. The interval between onset and death was rapid, usually within 6 hours in the nontreated group. On the other hand, some of the treated mice had a delayed time of death; 6 died 6 hours, 2 died 24 hours, and 1 died 48 hours after disease onset.

This study suggests the possibility of using T-705 as a therapeutic agent once RABV has penetrated the CNS, even at dosages below that reported in the postexposure prophylaxis experiment (300 mg/kg/day) by Yamada et al. It has been shown that RABV can remain dormant within the nervous system for weeks, during which infected individuals remain asymptomatic, with no neural deficits [1]. Further, T-705 at a higher dose may be able to delay the disease onset, thus providing time for the host to elicit sufficient immune responses or even rescue the infected host during the symptomatic stage.

Notes

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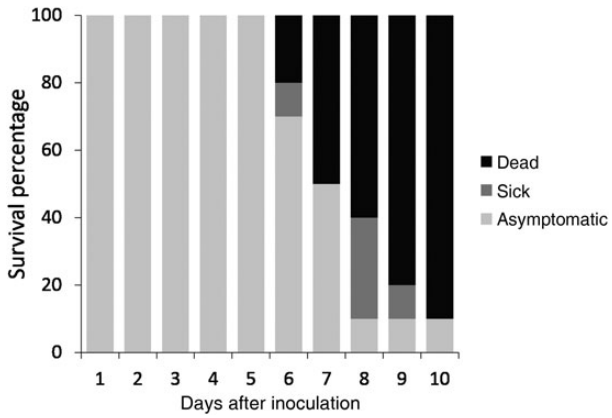

Figure 1. Results of oral T-705 administration in mice intracerebrally infected with rabies virus strain CVS-11.

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Phatthamon Virojanapirom,[1,2] Boonlert Lumlertdacha,[3] Aschariya Wipattanakitchareon,[2] and Thiravat Hemachudha[1,2]

[1]WHO Collaborating Centre for Research and Training on Viral Zoonoses, [2]Faculty of Medicine, Chulalongkorn University, and [3]WHO Collaborating Centre for Research on Rabies Pathogenesis and Prevention, Queen Saovabha Memorial Institute, The Thai Red Cross Society, Bangkok, Thailand

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Correspondence: P. Virojanapirom, WHO Collaborating Centre for Research and Training on Viral Zoonoses, Faculty of Medicine, Chulalongkorn University, Bangkok, 10330, Thailand (phatthamon@gmail.com).

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