Evodiamine is a Broad-spectrum Enterovirus Replication Inhibitor That Targets the Cellular Autophagy Pathway

Yi-Hsuan Chang[1*], Hsin-Sheng Su[1], Szu-Hao Kung[1]

[1.] National Yang-Ming University

Background/Objective

Enteroviruses 71 (EV71) belongs to the genus Enterovirus genus of the family Piconaviridae. EV71 infections commonly cause hand, foot and mouth disease and occasionally neurological manifestations in infants and young children. However, treatment of EV71 infections remains a significantly unmet medical need. Autophagy is a cellular catabolic process that becomes activated under stress conditions. It has been known that EV71 infections induce autophagy that promotes virus replication both in vivo and in vitro. In this study, we have attempted to investigate evodiamine (Evo), a main bioactive ingredient of a traditional medicine Evodia rutoecarpa, as an EV71 replication inhibitor due to its recent finding as an autophagy suppressor.

Method

Viral replications inhibited by the compound were investigated by a plaque assay and an immunofluorescence assay. Viral protein expressions were studied by a Western blot. Autophagy targeted by the compound was monitored by the ratio of microtubule- associated protein light chain 3 (LC3)-I to LC3-II as well as the formation of EGFP-LC3 punctae.

Result

Evo inhibited EV71 protein synthesis in a dose-dependent manner, and substantially protected infected cells from the cytopathic effects. Both Evo and it structural analogs rutaecarpine (Rut) exhibited antiviral effects that extended to other EV species, including coxsackievirus A16 and coxsackievirus B3. Moreover, Evo could significantly inhibit the accumulation of LC3-II and the punctate aggregation of EGFP-LC3, both are hallmarks of autophagy induced by EV71 infection. Finally, combinations of Evo and ribavirin, a known general RNA virus inhibitor, can synergistically inhibit viral replication while lowering the cytotoxicity caused by individual compounds.

Conclusion

In sum, we have provided evidences that enterovirus replication can be substantially suppressed by targeting autophagy, an essential cellular pathway induced by EV71 infection and required for viral replication. Evo might serve as a novel host-directed compound for broad-spectrum enterovirus therapy.