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(+)-*epi*-Clausenamide, but not (−)-*epi*-clausenamide, showed more potential than (−)-clausenamide on facilitating synaptic transmission in CA1 region of hippocampal synapses

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HIGHLIGHTS

- (+)-*epi*-clausenamide potentiated synaptic transmission in a dose dependent manner.
- Calcium influx was not involved in (+)-*epi*-clausenamide facilitating synaptic transmission.
- Excitatory transmitter release might play key roles in the mechanism.

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ABSTRACT

Effect of (+)-*epi*-clausenamide and (−)-*epi*-clausenamide on synaptic transmission in CA1 region of hippocampal slice was compared in this study. (+)-*epi*-Clausenamide showed more potency than (−)-clausenamide on either induction or maintenance of long term potentiation (LTP). Effect of (+)-*epi*-clausenamide on potentiating basic synaptic transmission was also superior to (−)-clausenamide. However, (−)-*epi*-clausenamide showed only slight effects on synaptic transmission, suggesting that the effect of (+)-*epi*-clausenamide and (−)-*epi*-clausenamide on synaptic transmission depended on their chirality. Calcium influx was not involved in (+)-*epi*-clausenamide facilitating synaptic transmission in this study. (+)-*epi*-Clausenamide might promote glutamate release through the activation of Synapsin I(Ser9) to activate the downstream effectors which play a key role in synaptic plasticity. Elucidating the mechanism of each optical isomer of clausenamide by electrophysiological methods provided basis for therapeutic strategies for neurological disorders.

Hippocampal long term potentiation (LTP) has been accepted to be a cellular model for synaptic plasticity [2]. Enhancement of hippocampal LTP has a physiological relevance in improvement of cognitive and memory deficits seen in dementia patients [17]. Recent studies showed that the chemically induced improvement of basal synaptic transmission in acute slices shared the similar mechanism with tetanic stimulation invoked LTP [19,20,22], suggesting a lower threshold to induce LTP or enhancement of LTP induction and maintenance [11]. Therefore, we observed the effects of our compounds on basic synaptic transmission and tetanic stimulation induced LTP.

Clausenamide, extracted from the leaves of Rutaceae *Clausena lansium* (lour) Skells, possesses 4 chiral centers. Previously, it was found that (−)-clausenamide potentiated synaptic transmission in rat hippocampus and improved cognitive dysfunction in dementia animal models, while (+)-clausenamide failed to have effects or even showed adverse effects [18,28,31], indicating that the possible receptors might possess a high degree of stereoselectivity toward (−)-clausenamide. The absolute configuration of *epi*-clausenamide is 3R,4S,5S,6S-(+)-*epi*-clausenamide and 3S,4R,5R,6R-(−)-*epi*-clausenamide, which is similar to clausenamide (3R,4S,5S,6R-(+)-clausenamide and 3S,4R,5R,6S-(−)-clausenamide) with the different arrangement of substituent at the carbon 6 in space (Fig. 1A). Stereisomers differ in pharmacokinetic and pharmacodynamic properties of enantiomers, and replacing existing racemates with single isomers always results in improved safety and/or efficacy profile of various racemates [4,10,23]. To further analyze the chirality dependent effects of those optically active clausenamide derivatives on synaptic transmission, we compared the effects of the enantiomeric pair of

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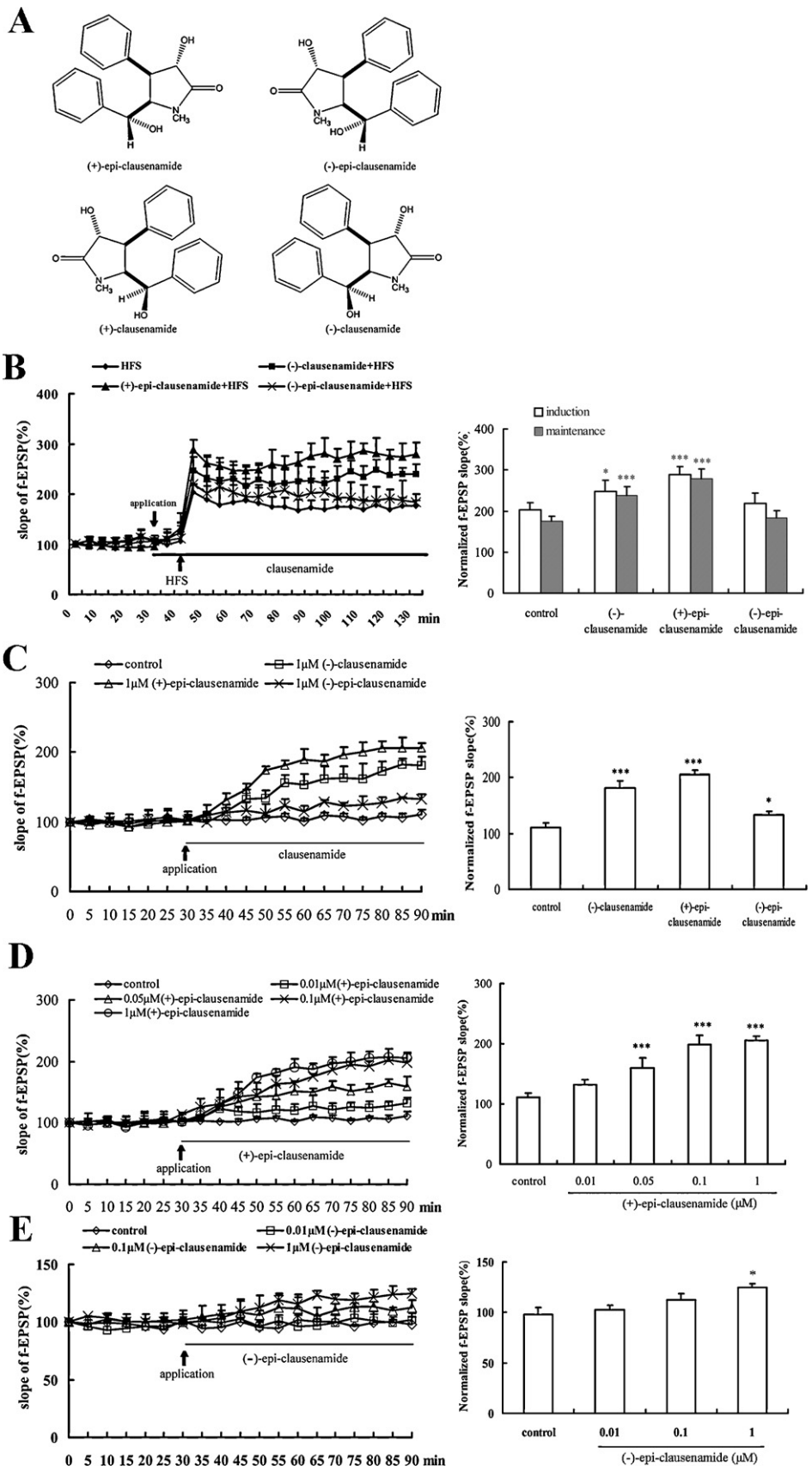

Fig. 1. Effect of (+)-*epi*-clausenamide and (−)-*epi*-clausenamide on basic synaptic transmission and LTP. (A) Chemical structure of *epi*-clausenamide and clausenamide. (B) Changes in the slope of f-EPSP following HFS are represented with or without application of (−)-clausenamide, (+)-*epi*-clausenmide or (−)-*epi*-clausenamide. (C) Changes in the slope of f-EPSP following application at 60 min in the presence or absence of (−)-clausenamide, (+)-*epi*-clausenmide or (−)-*epi*-clausenamide under test stimuli. Dose of (−)-clausenamide, (+)-*epi*-clausenmide or (−)-*epi*-clausenamide used above was 1 μM. (D) Changes in the slope of f-EPSP after application with (+)-*epi*-clausenamide of different concentration under test stimuli. (E) Effect of (−)-*epi*-clausenamide on slope of f-EPSP under test stimuli. Slope of f-EPSP at 60 min after treated is normalized ($n = 6$), and data were expressed as mean ± S.E.M. $^{*}P < 0.05$, $^{***}P < 0.001$ vs. control group.