THE SPINAL INHIBITION OF N-TYPE VOLTAGE-GATED CALCIUM CHANNELS SELECTIVELY PREVENTS SCRATCHING BEHAVIOR IN MICE

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ABSTRACT

The present study investigated the effects of pharmacological spinal inhibition of voltage-gated calcium channels (VGCC) in mouse pruritus. The epidural administration of P/Q-type MVIIC or PhTx3.3, L-type verapamil, T-type NNC 55-0396 or R-type SNX-482 VGCC blockers failed to alter the scratching behavior caused by the proteinase-activated receptor 2 (PAR-2) activator trypsin, injected into the mouse nape skin. Otherwise, trypsin-elicited pruritus was markedly reduced by the spinal administration of preferential N-type VGCC inhibitors MVIIA and Phα1β. Time-course experiments revealed that Conus magus-derived toxin MVIIA displayed significant effects when dosed from 1h to 4h before trypsin, while the anti-pruritic effects of Phα1β from Phoneutria nigriventer remained significant for up to 12h. In addition to reducing trypsin-evoked itching, MVIIA or Phα1β also prevented the itching elicited by intradermal (i.d.) injection of SLIGRL-NH2, compound 48/80 or chloroquine, although they did not affect H2O2-induced scratching behavior. Furthermore, the co-administration of MVIIA or Phα1β markedly inhibited the pruritus caused by the spinal injection of gastrin-releasing peptide (GRP), but not morphine. Notably, the epidural administration of MVIIA or Phα1β greatly prevented the chronic pruritus allied to dry skin model. However, either tested toxin failed to alter the edema formation or neutrophil influx caused by trypsin, whereas they significantly reduced the c-Fos activation in laminas I, II and III of the spinal cord. Our data bring novel evidence on itching transmission mechanisms, pointing out the therapeutic relevance of N-type VGCC inhibitors to control refractory pruritus.

Keywords: