

## Excitatory effect of KR-25018 and capsaicin on the isolated guinea pig bronchi

정이숙<sup>o</sup>, 신화섭<sup>\*</sup>, 박노상<sup>\*</sup>, 문창현, 조태순<sup>†</sup>

아주대 의대, <sup>\*</sup>한국화학연구소, <sup>†</sup>성균관대 약대

We investigated the peripheral excitatory effect of capsaicin and KR-25018, a newly synthesized capsaicin derivative which was demonstrated to have a potent analgesic activity. KR-25018 and capsaicin were found to be both potent efficacious contractors of isolated guinea pig bronchial smooth muscle. KR-25018 was equipotent with capsaicin and [Sar<sup>9</sup>,Met(O<sub>2</sub>)<sup>11</sup>]-substance P, 10-fold more potent than histamine and 10-fold less potent than [ $\beta$ -Ala<sup>8</sup>]-neurokinin A(4-10), and their  $-\log(M)EC_{50}$  values were  $6.94 \pm 0.08$ ,  $6.86 \pm 0.05$ ,  $6.96 \pm 0.07$ ,  $5.64 \pm 0.04$ ,  $7.96 \pm 0.02$ , respectively. Contractile responses to KR-25018 and capsaicin were potentiated by phosphoramidon ( $1 \mu M$ ), an inhibitor of neuropeptide-inactivating endopeptidase, but completely abolished in a calcium-free medium. These responses to KR-25018 and capsaicin were unaffected by the NK-1 antagonist CP96345 ( $1 \mu M$ ), partially inhibited by the NK-2 antagonist SR48968 ( $1 \mu M$ ) but almost completely abolished by a combination of the antagonists. A vanilloid receptor antagonist capsazepine competitively antagonized the responses to both KR-25018 and capsaicin ( $pA_2$ : against KR-25018,  $5.98 \pm 0.47$ ; against capsaicin,  $5.80 \pm 0.31$ ), and a capsaicin-sensitive cation channel antagonist ruthenium red caused significant reduction in the maximum responses to KR-25018 and capsaicin ( $pD'_2$ : against KR-25018,  $4.61 \pm 0.33$ ; against capsaicin  $4.96 \pm 0.21$ ). In conclusion, the present results suggest that KR-25018 and capsaicin act on the same vanilloid receptor inducing the influx of calcium through ruthenium red-sensitive cation channel and produce contractile responses via the release of tachykinins that act on both NK-1 and NK-2 receptor subtypes.