

KRP-204, A SELECTIVE BETA3-ADRENOCEPTOR AGONIST, SUPPRESSES LICKING BEHAVIOR INDUCED BY INTRAVESICAL INSTILLATION OF CAPSAICIN IN RATS

Hypothesis / aims of study

Beta3-adrenoceptor (AR) agonists are considered to be useful for the treatment of overactive bladder because they have a relaxant effect on the rat and human detrusor muscle, and increase bladder capacity in rats [1]. However it remains unclear whether or not beta3-AR agonists have a suppressive effect on the afferent pathway from the lower urinary tract. It has been reported that rats intensely licked their abdomen following intravesical instillation of capsaicin, and this behavioral response was mediated by capsaicin-sensitive, unmyelinated C-fiber [2]. Therefore, we examined whether KRP-204, a selective beta3-AR agonist ($EC_{50}=1.7$ nM, in CHO cells expressing human beta3-AR [3]), acts on C-fiber afferent nerves by observing the licking behavior induced by intravesical instillation of capsaicin in rats.

Study design, materials and methods

Seven days before the experiment, male Wistar rats were anesthetized with Halothane and catheters were implanted in the bladder dome for capsaicin instillation as well as in the stomach or femoral vein for drug administration. Catheters were tunneled subcutaneously and exteriorized dorsally.

On the day of the experiment, rats were placed in transparent 30x20x12 cm cages for quantification of the licking behavior, which was defined by the length of time the rats licked (groomed) their bodies, excluding their paws and tail, during a defined observation time period. As a primary challenge, saline was infused into the bladder at the rate of 10 ml/hr for 30 min. After saline infusion, 30 microM capsaicin was infused at the same rate, and the time length of licking behavior was measured for 30 min. A secondary challenge, consisting of the same steps, was performed two hours later. Drugs were administered before the secondary challenge, and their effects were assessed by expressing the licking behavior during the secondary challenge as a percentage of the primary challenge.

Results

The time length of the licking behavior was increased by instillation of capsaicin in a concentration-dependent manner, and 30 microM capsaicin induced the maximal response. The licking behavior was particularly intense following voiding, and was not statistically different between the primary and secondary challenges. Capsaicin-induced licking behavior was completely abolished by systemic capsaicin pretreatment (125 mg/kg s.c. for 3 days). The time length of the licking behavior was significantly reduced by KRP-204 in a dose-dependent manner, and the value at 3 mg/kg group was 75.7% (Fig 1). Further the reducing effect of KRP-204 was abolished by pretreatment with SR59230A, a selective beta3-AR antagonist. Isoproterenol, a non-selective beta-AR agonist, also suppressed the time length of the licking behavior, and this effect was also abolished by pretreatment with SR59230A. In contrast, tolterodine, a muscarinic receptor antagonist, had no effect on the time length of the licking behavior induced by capsaicin.

Interpretation of results

The capsaicin-induced licking behavior was completely abolished by C-fiber desensitization that was induced by systemic capsaicin pretreatment, suggesting that this response is mediated by capsaicin-sensitive C-fiber. The licking behavior in rats was particularly intense after voiding, indicating that the behavioral response to capsaicin may be produced by stimulation of urethral afferents rather than bladder afferents as previously reported [2]. KRP-204 as well as isoproterenol suppressed the licking behavior, and their effects were abolished by SR59230A. Taken together, our data suggest that KRP-204 suppresses the C-fiber urethral afferent activity via beta3-AR. Since stimulation of the proximal urethra causes urgency, administration of KRP-204 may have a beneficial effect.

Concluding message

KRP-204 suppressed the licking behavior induced by intravesical instillation of capsaicin in rats via beta3-AR, suggesting that KRP-204 has a suppressive effect on C-fiber urethral afferent nerves.

References

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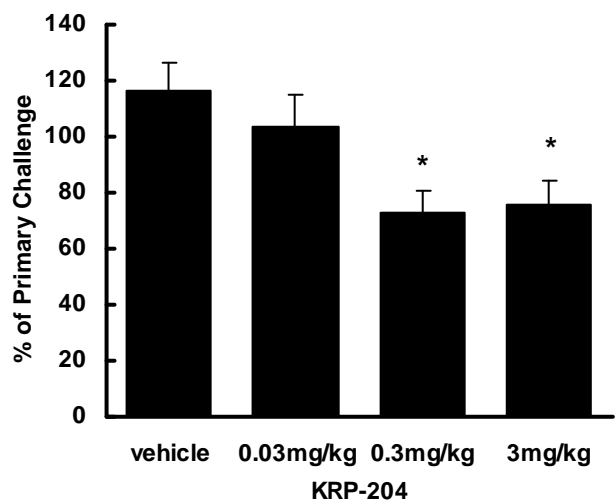


Fig 1. Effect of intragastrical administration of KRP-204 on the licking behavior induced by intravesical instillation of capsaicin. KRP-204 was administered intragastrically two hours before the secondary challenge. Data are shown as mean \pm SEM (n = 4-5). Dunnett's test was used for analysis. * p<0.05.

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