CARACTERIZAÇÃO DO PAPEL DA FOSFATIDILINOSITOL-3 QUINASE γ NAS RESPOSTAS INFLAMATÓRIAS E NOCICEPTIVAS INDUZIDAS PELA TRIPSINA EM CAMUNDONGOS

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Resumo

Introduction: It has been described that PI3Kγ plays a pivotal role in inflammation, and it is involved in chronic inflammation and autoimmune diseases. This study investigated the effects of selective PI3Kγ inhibitors in the nociceptive, inflammatory and pruriceptive responses induced by different pro-inflammatory agents in mice. Methods: Male Swiss mice (8 per group, 25-30 g) were used. All the experimental protocols were approved by the Local Ethics Committee (09/00101-PUCRS). Mice were treated orally with the selective PI3Kγ inhibitors AS605240 (1 to 30 mg/kg), AS041164 and AS252424 (both 1 mg/kg), 30 min before. The control groups received saline. Edema was induced by an intraplantar (i.pl.) injection of the protease trypsin (30 µg/paw, 50 µl) in the right hindpaw. The left paw received 50 µl of saline. Edema was determined with a plethysmometer, at different periods of time (0.5 to 6 h). Another parameter analyzed was the scratching behavior evoked by trypsin (200 µg/site, 50 µl) or by the mast cell depletor CP48/80 (10 µg/site, 50 µl) in the mouse dorsum. Scratching was measured for 40 min, as the number of scratches with forepaws and hindpaws close to the injected site and/or behind the ears. For evaluating spontaneous nociception, mice received an i.pl. injection of trypsin (300 µg/paw, 20 µl) or the active red pepper principle capsaicin (1.6 µg/paw, 20 µl) into the right hindpaw, and the amount of time (in s) spent licking and/or biting the injected paw was recorded during 10 min. Results: AS605240 administered orally produced a significant and dose-dependent reduction of paw edema induced by trypsin. The percentages of inhibition, calculated based on the area under the curve, were: 24 ± 7%, 46 ± 3%, 40 ± 7% and 42 ± 3%, for the doses of 1, 3, 10 and 30 mg/kg, respectively. In addition, the treatment with AS605240 produced a marked
reduction of scratching behavior elicited by trypsin (200 µg/site). The inhibition percentages were 60 ± 8%, 57 ± 12% and 51 ± 8% for the doses of 1, 3 and 10 mg/kg, respectively. However, the administration of AS041164 and AS252424 was not able to significantly affect trypsin-induced scratching response. Moreover, AS605240 (1 mg/kg) was also capable to produce a partial, but significant inhibition of the scratching bouts elicited by CP 48/80 (25 ± 6%). Finally, AS605240 promoted a significant reduction of spontaneous nociception induced by trypsin in the mouse paw, at the dose of 1 mg/kg (61 ± 7 %). On the other hand, a higher dose of AS605240 (10 mg/kg) did not significantly alter this response. Likewise, the administration of AS605240 (1 mg/kg, 30 min) did not modify capsaicin-evoked nociception.

**Discussion:** The present results suggest that AS605240 was the most effective PI3Kγ inhibitor in the inflammatory and nociceptive models tested herein. It is tempting to suggest that this compound might well represent a promising alternative for treating inflammatory-related painful conditions.

**Referências**

