Scratching behaviour elicited by endothelin-1 in the mouse cheek model

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Itch, a frequent and sometimes severe symptom in skin and other diseases, is a sensation mediated by distinct neural circuits and multiple mediators. Intradermal (i.d.) injection of endothelin-1 (ET-1), into the scruff of the neck, causes scratching behavior suggestive of overt pruritus. This study assesses the role of ETA and ETB receptors in ET-1-induced pruritus in the “mouse cheek model” proposed by Shimada and LaMotte (2008), which discriminates pruritus from nociception, as well as some mechanisms which modulate the response to ET-1.

Male 2-month old CD1 mice had both cheeks shaved. Two days later, each mouse received an i.d. injection of ET-1 (3, 10, 30 pmol) or vehicle (20 µl) into the left cheek. The number hind paw scratching bouts, directed to the injected cheek, were filmed and counted over 40 min. In some experiments, BQ-123 and/or BQ-788 (ETA or ETB receptor antagonists, respectively; 10 nmol, i.d.) were injected 5 min prior to ipsilateral ET-1 (30 pmol) injection. In others, ET-1 was co-injected together with antagonists for µ (CTOP, 20 nmol), κ (Nor-BNI, 68 nmol) or δ opioid receptors (Naltrindole, 80 nmol), or agonists for µ (DAMGO, 100 nmol) or κ receptors (U50488-H, 100 nmol). Alternatively, loratadine (histamine H1 receptor antagonist; 10 mg/kg, intraperitoneally) was injected 1 h before ET-1. In another experiment, the cheek was removed 15 min after i.d. ET-1 or vehicle injection, and the number of degranulated mast cells was quantified by histology in 7 µm sections stained with Toluidine Blue. The study was approved by UFSC’s Ethics Committee on Animal Use.

Injection of ET-1 promoted dose-dependent bouts of scratching (30 pmol: 49 ± 3 bouts). Treatment with BQ-123 prior to ET-1(30 pmol) reduced scratching (9 ± 3 bouts), whereas BQ-788 increased them (82 ± 10 bouts). Co-injection of both antagonists resulted in significantly less scratching bouts than that recorded following BQ-788 + ET-1(13 ± 2 bouts). Co-injection of CTOP or Nor-BNI, together with ET-1, increased scratching responses by 54% and 24 %, respectively. Naltrindole did not modify the scratching response to ET-1. The µ-selective opioid agonist DAMGO reduced the scratching bouts by 50 %, but the selective κ agonist U-50488H was not effective. Loratadine reduced the scratching bouts by 22%. Cheek skin sections obtained 15 min after ET-1 showed more degranulated mast cells than vehicle-treated controls.

These results confirm in the mouse cheek model that ET-1 induces ETA receptor-mediated pruritus and that ETB receptors limit this response. The pruritogenic response to ET-1 seems to be modulated by endogenous opioids activating local µ opioid receptors in this model, but the role of κ receptors in controlling scratching remains to be better characterized. This pruritogenic response seems to be modulated only partially by histamine and coincides in time with local mast cell degranulation.

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