

Table S1. Outline of the available methods to perform experimental induction of itch mediated by histaminergic as well as non-histaminergic mechanisms

Itch model	Study	Method of application (mainly used)	Peak itch intensity	Alloknesis	Hyperknesis	Hyperalgesia	Vasomotor response	Other findings
Electrical	(10)	0.1×7 mm electrode, stimuli: 0.08–8 ms and 2–200 Hz, 0–0.38 mA	4.5 (NRS 0–10)	✓ (3 cm)	✓ (1.5 cm)	Very modest	Very modest	Reported pain at the peak itch-evoking stimulus was 2.2 (NRS 0–10). The study included patients with AD, but found no significant difference in any response parameters. Hyperalgesia and allodynia were almost undetectable: ≥ 1 (radius, cm).
Mechanical	(54)	4×3.5 cm electrode, stimuli 0.3 ms, 100 Hz and 0.2–15 mA	1.5 (VAS 0–10)	N/A	N/A	N/A	N/A	Investigated the effect of conditioning itch stimuli (histamine-iontophoresis) and found that pruritic conditioning stimulation is impaired in chronic itch patients (psoriasis). Notice the low reported itch intensity of 1.4 (VAS 0–10).
	(55)	Vellus hair vibration, 1–50 Hz, 0–1 mm amplitude only	5 (VAS 0–10) on chin	✓	N/A	N/A	No wheal or flare	Alloknesis was only recorded as an itch induction rating, by mechanical stimulation 1 cm away from the vibration stimulation spot, not as a quantified area.
Histamine	(27, 80)	Intradermal and subcutaneous injections, 0.10, 1, 10 µg histamine	50–60 (NRS 0–100)	✓ (28–46 cm ²)	N/A	N/A	Significant wheal and flare	Includes detailed results on itch latency as a function of injection depth and skin temperature, shown that heat stimulation and superficial injection produces a faster onset of itch.
	(14)	Iontophoresis, 1% histamine solution, 200 µA, 14 Ø electrode	35–40 (VAS 1–100)	N/A	N/A	N/A	N/A	Histamine produced far less intense itch than cowhage spicules in both healthy controls and patients with AD. Co-stimulation of histaminergic and cowhage-itch pathways did not result in a summation of itch intensity.
	(23)	Single spicules, 0.01–100 mg/ml (10 mg/ml)	"Moderate" (gLMS)	✓ (11 cm ²)	✓ (15 cm ²)	✓ (8 cm ²)	Wheal + flare present at ≥ 10 mg/ml	Histamine produced itch and nociceptive sensations comparable to native cowhage spicules, but with wheal and flare occurring at higher concentrations. Punctate delivered histamine cause a more rapid spike in itch than iontophoresis delivery.
	(11)	Intradermal injection, 1 µg of histamine phosphate (mosquito-bite) in 10 µl vehicle	1.5–2×modulus	N/A	N/A	N/A	Significant wheal and flare	Showed that capsaicin pretreatment only partially reduced histaminergic itch, highlighting that histaminergic itch can be conveyed independently of TRPV1.
Punctate capsaicin	(23)	Single spicules, concentrations 1–200 mg/ml (200 mg/ml)	"Weak" to "strong" (gLMS)	✓ (6.5 cm ²)	✓ (10 cm ²)	✓ (7.5 cm ²)	Flare present (29%) at 200 mg/ml	Produces less itch and more pricking/stinging pain than punctate histamine and native cowhage spicules. Capsaicin produces less alloknesis than histamine and native spicules, but comparable areas of hyperknesis and hyperalgesia.
Cowhage	(31)	"Cowhage inserter", 1, 7, 28 spicules, 1 cm ² area	"Moderate" to "intense" (gLMS)	✓ (16–35 cm)	✓ (16–39 cm)	✓ (11 cm)	None/(modest in 6/45)	Detailed outline of the somatosensory effects of cowhage. Reports weak to moderate concomitant sensations of pricking and burning. No summation within a region of 1×0.1 cm, but considerable summation in a 11×0.1 cm application area.
	(14)	40–45 spicules rubbed onto a 4 cm ² area=13–15 spicules inserted	60–65 (VAS 1–100)	N/A	N/A	N/A	N/A	Compared cowhage-induced itch between AD patients and HC. Itch intensity exhibited no difference, but the itch persisted for longer in the AD group.
	(23)	Single spicules inserted by forceps	"Moderate" to "strong" (gLMS)	✓ (18 cm ²)	✓ (15 cm ²)	✓ (10 cm ²)	No wheal or flare	Combinatorial application of cowhage and histamine did not increase the itch intensity.
BAM8-22	(15)	Three spicules inserted; 0.004, 0.04, 0.4 & 4 mg/ml solution (4 mg/ml)	"Moderate" to "strong" (gLMS)	✓ (10 cm)	✓ (9 cm)	✓ (11 cm)	No wheal or flare	Compared the somatosensory effect of insertion of singles spicules; native cowhage, histamine loaded and capsaicin loaded.
β-alanine	(68)	Intradermal injection 10 µl with 22.5, 45, 90, or 180 µg	"Weak" to "moderate" (N/A)	N/A	N/A	N/A	No wheal or flare	Showed that the proenkephalin A-derivative BAM8-22 is a potent itch inducer and, notably, that both BAM8-22-induced itch and associated dysesthesias are refractory to pretreatment with antihistamine.
Serotonin	(81)	Iontophoresis, 1% serotonin solution, 1 mA	3 (VAS 0–10)	✓ (90 cm ²)	✓ (90 cm ²)	✓ (90 cm ²)	No wheal, significant flare	A series of experiments elucidated MrgprD as the receptor for β-alanine and showed the β-alanine responsive neurons were of the CMH-class and irresponsive to histamine.

AD: atopic dermatitis; BAM8-22: bovine adrenal medulla 8–22 peptide; gLMS: generalized labelled magnitude scale; HC: healthy controls; N/A: not assessed; VAS: visual analogue scale; NRS: numerical rating scale; TRPV1: transient receptor potential vanillin 1; MrgprD: Mas-related G-protein coupled receptor member D; CMH: C-mechano-heat.