

Neurological itch

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”A half-century of neurotransmitter research”

- ◆ Previously ”The sparks” and ”the soup” theory
- ◆ ”Sparks” –electrical signal transduction in the CNS
- ◆ ”The soup” in the periphery - chemical mediator transmission
- ◆ Fluorescence histochemical method of Falck and Hillarp could demonstrate neuronal localization of dopamine, noradrenalin and serotonin pointing to chemical transmission within the CNS
- ◆ CARLSSON A, FALCK B, HILLARP NA. Cellular localization of brain monoamines. Acta Physiol Scand Suppl. 1962;56(196):1-28



Histology Department, Lund

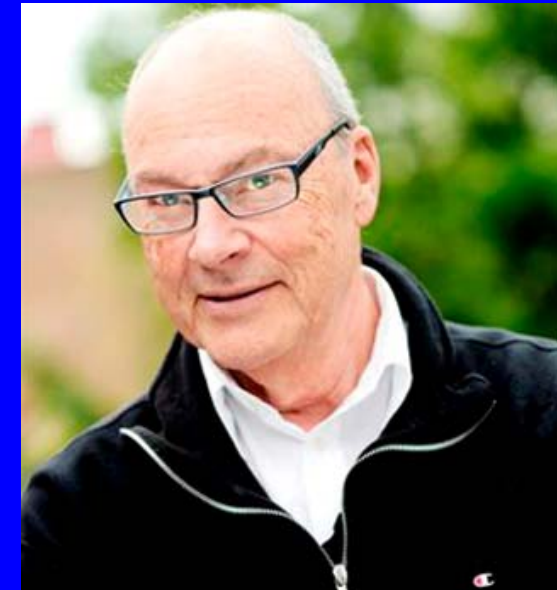
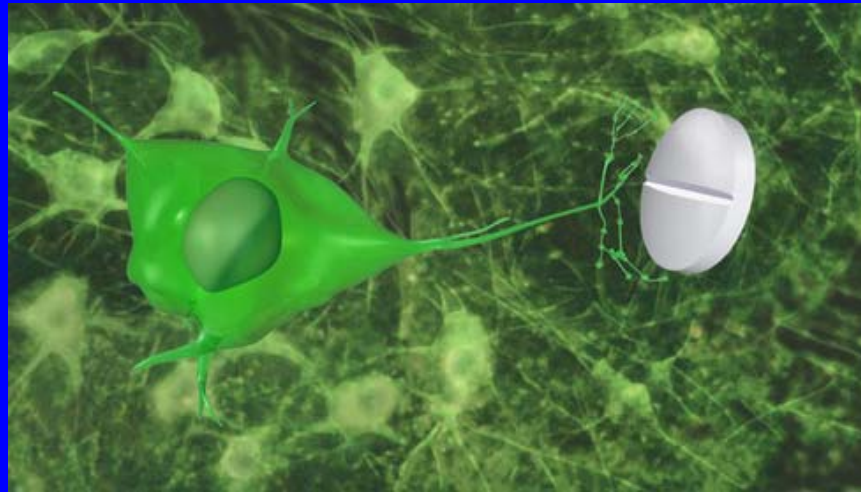
- ◆ ” The major monoaminergic pathways could be mapped, and the site of the major psychotropic drugs clarified.” (A. Carlsson, Nobel Lecture, 2000)



”From nerve to pill”

Symposium, April 27th, 2012, Lund

To celebrate 50 years with Falck-Hillarp method



Frank Sundler

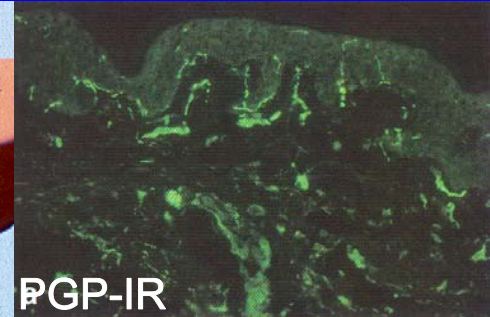
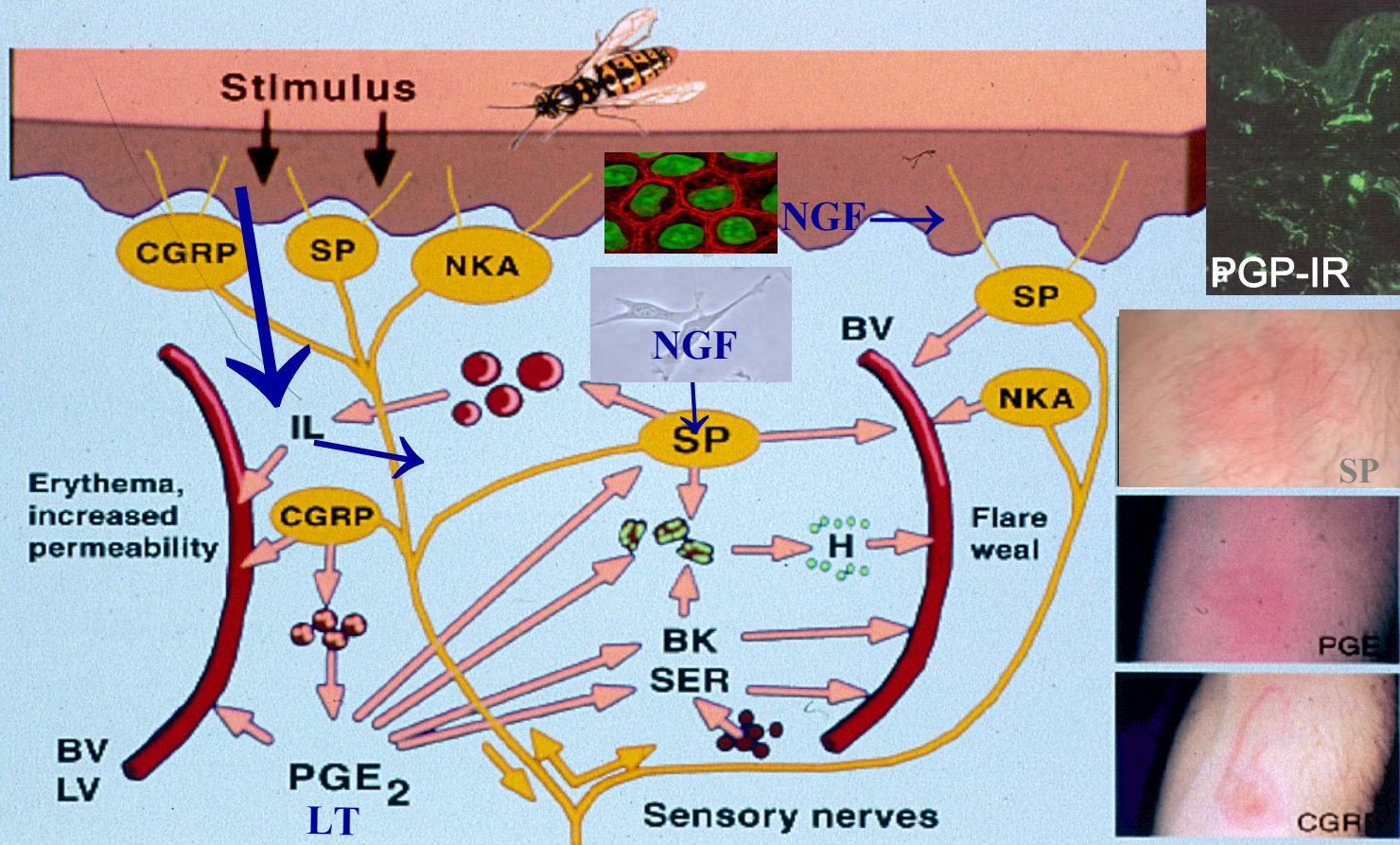
Rolf Håkanson

Prozac, Citalopram, L-Dopa, Omeprazol



Transmission of itch in the skin

Dermal nociceptive itch and neurogenic inflammation



Mechano-insensitive C-fibers
receptor territories 85 mm diameter, conduction velocity 0,5 m/sec



Spontaneous approaches to combat itch

Approaches that are consistent in different diseases:

- ◆ Urticaria – *rubbing* of the skin
 - ◆ Atopic eczema, scabies and other inflammatory skin disorders – *scratching*
 - ◆ Prurigo nodularis – *digging* the skin
 - ◆ Brachioradial pruritus – putting *ice cubes*
-
- ◆ Different mediators responsible?
 - ◆ Different pathways involved?
 - ◆ Burning, stubbing, electric shock, paresthesia → neuropathic itch



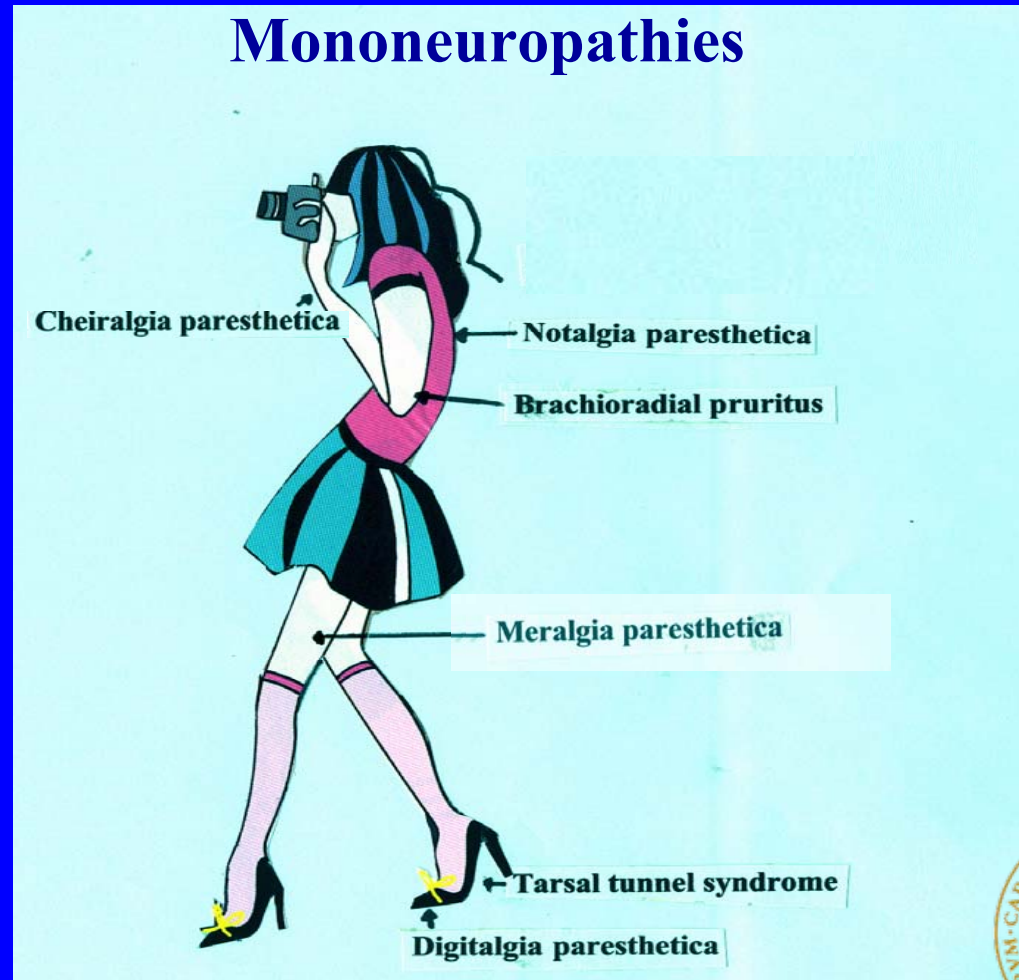
Localized itch disorders

”dysesthetic dynias” and ”- paresthetic algias”

◆ Scalp dystesthesia

◆ Glossodynia
(Burning mouth syndrome)

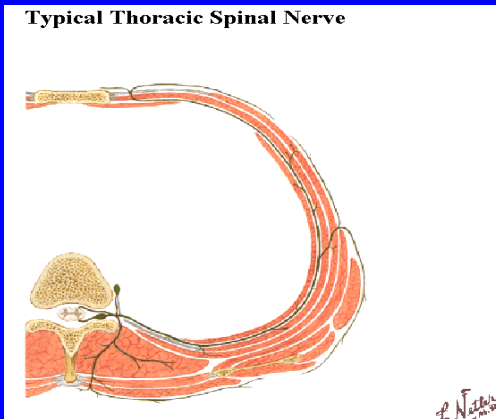
◆ Vulvodynia /
scrotodynia



Notalgia paresthetica



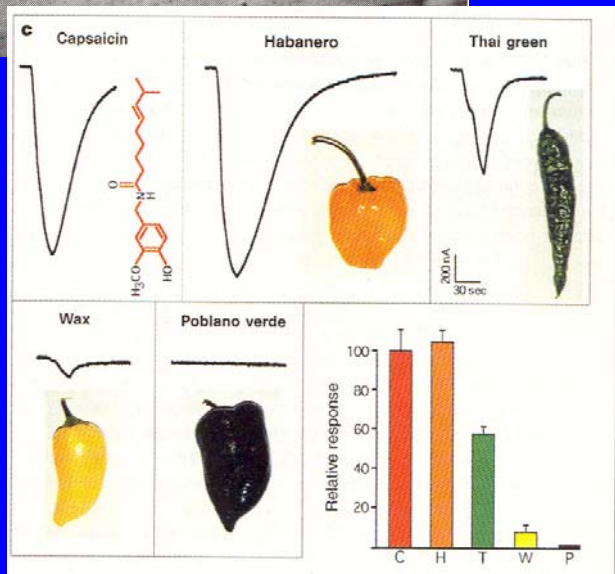
- ◆ Focal, intense, burning itch on the medial scapular border (Astwazaturow, 1934).
- ◆ Thoracic nerves (T2-T6) penetrate the spinae muscle in a right angle course which predisposes them for injury from mild insults.



Notalgia paresthetica



- ◆ Itch and paresthesia confined to C4 dermatome, MRI in the right C3 - C4 intervertebral space, impingement of the C4 nerve root (Eisenberg, 1997).

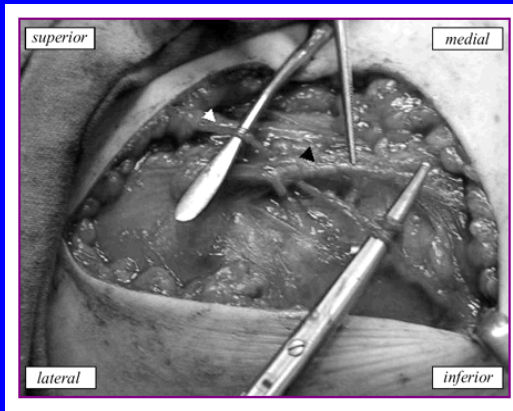
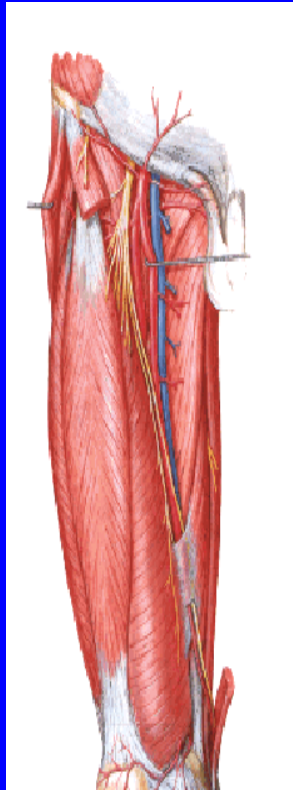


- ◆ Increased number of dermal nerve fibers (Springall, 1991).
- ◆ Depletion of neuropeptides from nerve fibers by capsaicin as therapy

Caterina 1997, Nature



Meralgia paresthetica



- ◆ Burning, tingling, numbness on the anterolateral thigh
- ◆ Entrapment neuropathy of lateral femoral cutaneous nerve of a soccer player (Ulkar, 2003)
- ◆ Decompression - the fibrous band was released by dissection
- ◆ Obesity, pregnancy, backpacking



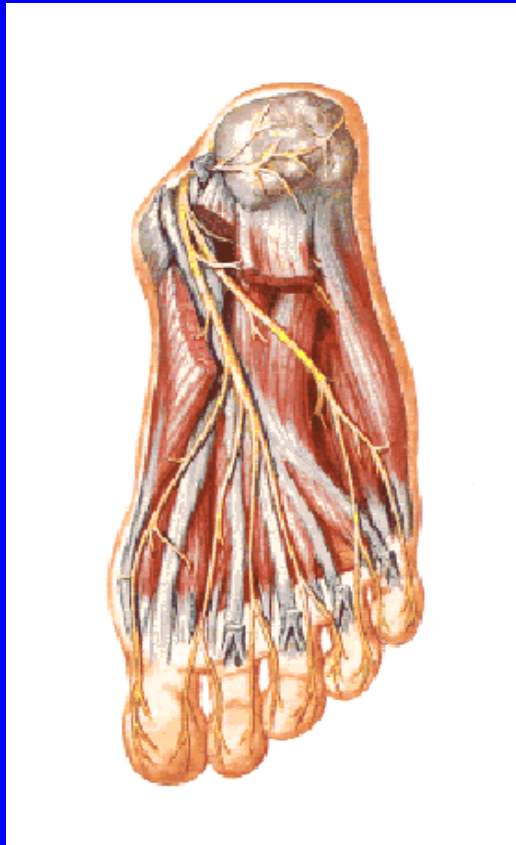
Backpacking – induced paresthesias



- ◆ Meralgia, digitalgia paresthetica and tarsal tunnel syndrome most common
- ◆ Paresthesias were reported in 96 of 280 long-distance backpackers
- ◆ Significant risk factor > 2000 miles, symptoms resolved following hiking (Boulware, 2003)



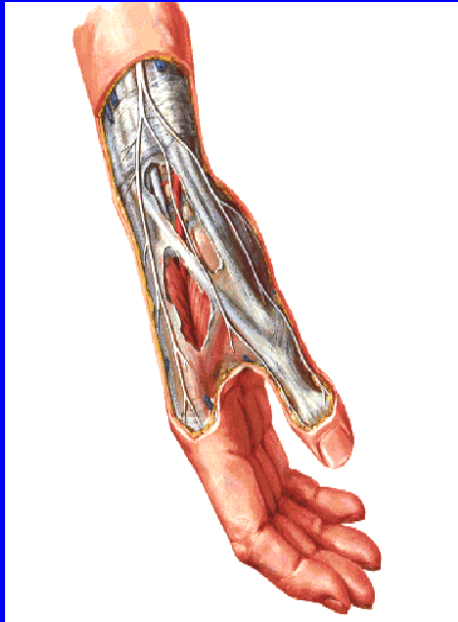
Marcher's digitalgia paresthetica



- ◆ **Digitalgia paresthetica**
(Wartenberg, 1954)- numbness of toes (or fingers)
- ◆ **Tarsal tunnel syndrome, a lesion of the posterior tibial nerve due to repetitive dorsiflexion of the ankle**
- ◆ **Burning around the ankles and lower legs**
- ◆ **In Israeli military recruits (14 of 30), mean time of onset - fourth week of training. Nine month follow up most were asymptomatic (Stein, 1989)**



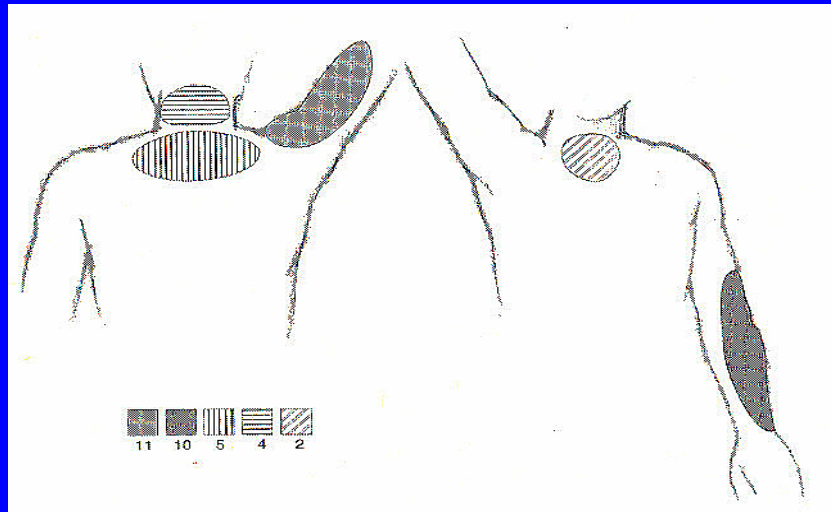
Cheiralgia paresthetica



- ◆ Radial nerve derived pain/itch (Wartenberg, 1932)
- ◆ Two cases that occurred secondary to handcuff placement (Massey, 1978)
- ◆ If no trauma, diabetes mellitus should be excluded



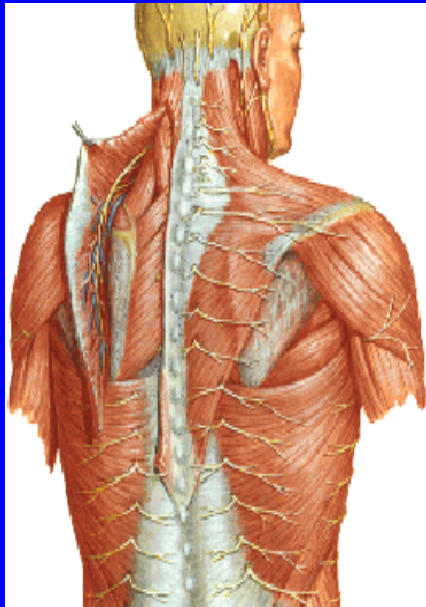
Brachioradial pruritus



- ◆ Tingling, burning sensation on arms and shoulders (“Solar pruritus of the elbows”, Weisman, 1968)
- ◆ A frequent presence of neck pain and spinal pathology (C5-7) shown radiologically, suggest cervical spine disease to be a predisposing factor (Heyl, 1983)
- ◆ There has been controversy regarding the cause of brachioradial pruritus ever since



Brachioradial pruritus; photoneuropathy or spinal disease?



- ◆ Two studies from Hawaii on 42 patients (Walcyk and Elpern, 1986) and on 68 patients (Knight and Hayashi 1994) suffering from itch all year. Exposure to sunlight was suggested as being the cause.
- ◆ In many patients living in temperate climates pruritus appears during the summer, remits in the winter and relapses the following summer.
- ◆ Report on 22 patients, review of literature on brachioradial pruritus: 30 of 98 patients suffered from cervical spine disease Goodkin Wingard, Bernhard 2003).



PUVA-pain

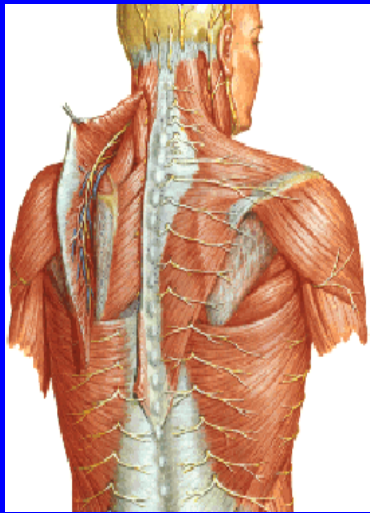


”Severe skin pain lasting one or two months occurred in 8 of 210 patients treated with PUVA. The pain started 4--8 weeks after the initial dose, mostly about one week after discontinuation of the treatment. It was a prickling, burning pain, usually coming in bouts and confined to limited areas "deep under the skin". In some respects the pain was related to itching, but the patients could easily distinguish between the two sensations.”

Tegner E. Severe skin pain after PUVA treatment. *Acta Derm Venereol.* 1979;59:467-470.



PUVA pain; an "over-dose" of UV, spinal disease or double crush?



- ◆ Improvement by physiotherapy

Roelandts R, Stevens A. PUVA-induced itching and skin pain. *Photodermatol Photoimmunol Photomed.* 1990; 7: 141-142.

- ◆ Double crush syndrome?

The distal part of an axon is easily damaged when another part of that axon is under compression.

Upton AR, McComas AJ. The double crush in nerve entrapment syndromes. *Lancet* 1973; 2: 359-362

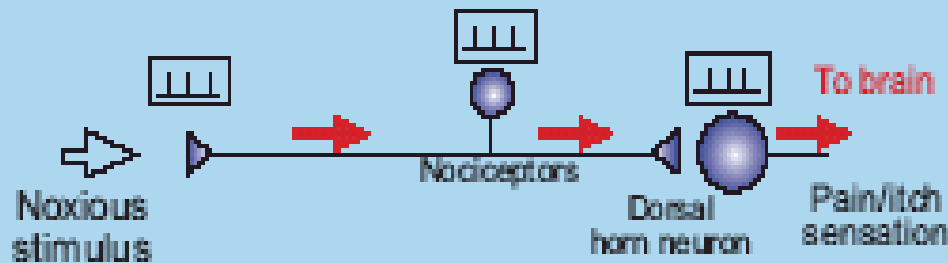
115 patients with carpal tunnel syndrome, 81 of them exhibited clinical symptoms of a neural lesion of the neck



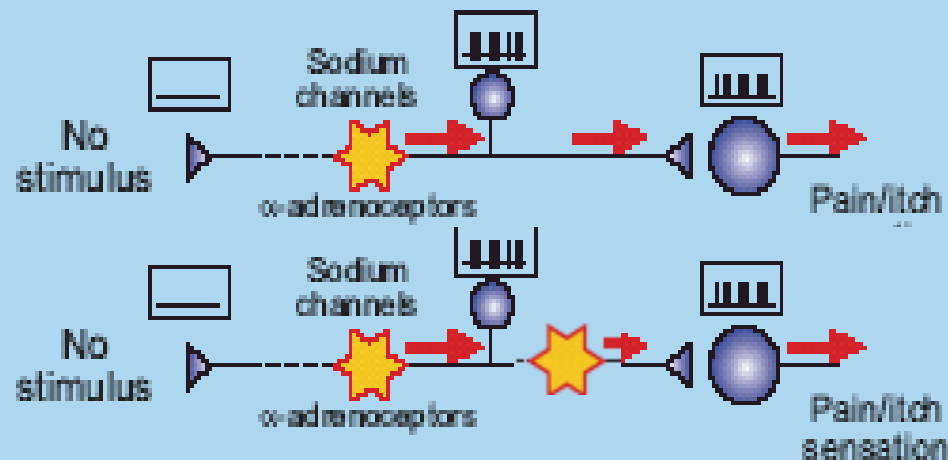
"Grenz sensations": between pain (algia) and itch (paresthetica)

Neuropathic, stimulus-independent itch

Normal sensory function



Sensory function after nerve injury with spontaneous firing along axon

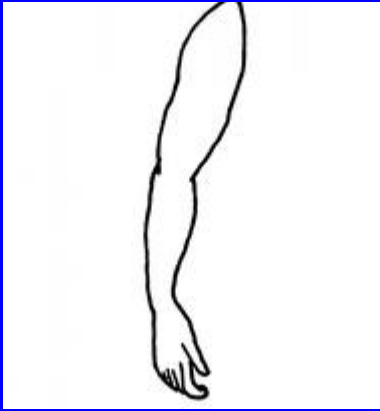


Brachioradial pruritus,
Entrapment neuropathies:
notalgia paresthetica etc

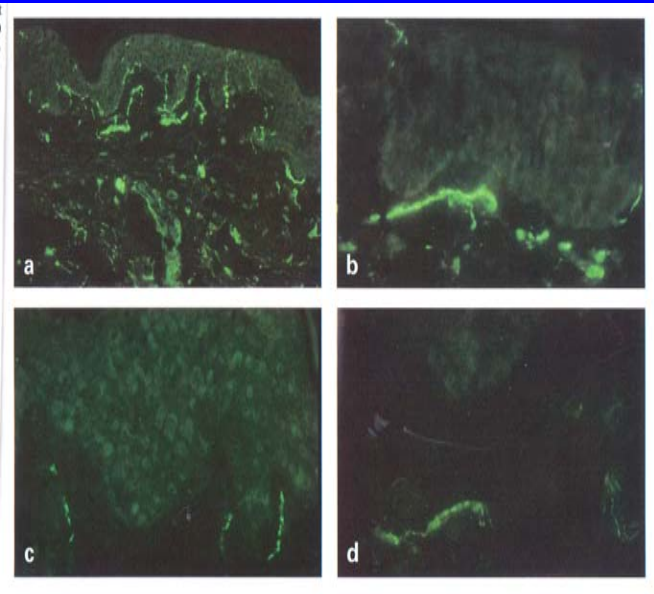
Double crush syndromes



Self healing photoneuropathy occurring in middle aged adults predisposed by cervical arthrosis.



- ◆ Four sisters with pruritus on arms (upper, lower or both) every summer
- ◆ The sisters spent much time outdoors and exposed themselves extensively
- ◆ Occupations requiring heavy lifting.
- ◆ Cervical radiographs indicated arthrosis (C5-C7)
- ◆ The density of sensory nerve fibers in the skin biopsies from the itchy skin of the arms (PGP9.5) was reduced compared with biopsies from the same skin region during the symptom-free period in the winter
- ◆ Wallengren J, Dahlbäck K. Familial brachioradial pruritus. *Br J Dermatol.* 2005;153(5):1016-8



Brachioradial pruritus (BRP)

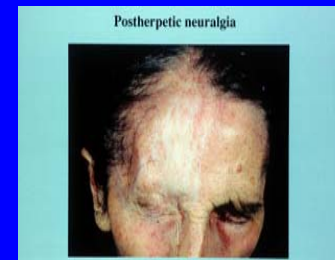
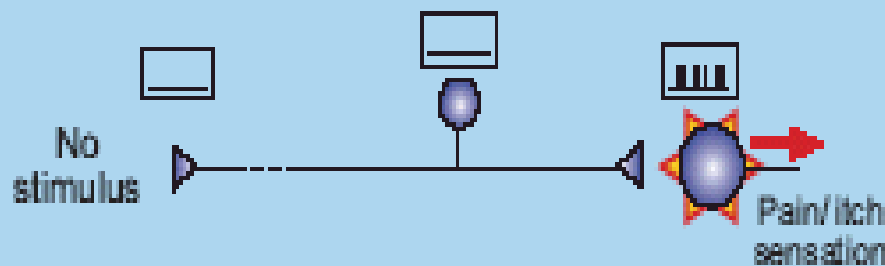


- ◆ ...I hope this relieves the itch for a while. I too want to rip the skin off of my arms or get an injection somehow, filled with lidocaine, and numb the nerves. The itch is from within. People don't understand how deep this itch is. It is soooooo frustrating that doctors don't know anything about this or care to find out how to cure this. I also take anti-depressants and I'm still itching. I hope that relaxing the trapezius muscle relieves any pinched nerves. All I wish for Christmas is to get rid of this hell of an itch!



Localized itch due to spinal injury

Sensory function after nerve injury with spontaneous firing of dorsal horn neurons in spinal cord



- ◆ Postherpetic neuralgia – lesion in ganglia
- ◆ Thalidomide-induced paresthesia in the lower legs is due to a lesion in the dorsal horn of the spinal cord



Scalp dysesthesia



- ◆ Chronic severe pain and/or pruritus of the scalp only without objective physical findings
- ◆ Study on eleven women (36 to 70 y)
- ◆ 5 women described pain, stinging, or burning only
- ◆ 4 women complained of pain and pruritus
- ◆ 2 women reported pruritus only
- ◆ Duration of symptoms ranged from 9 months to 7 years.
- ◆ Five women had physician-diagnosed psychiatric disorders, including generalized anxiety, and somatization
- ◆ Seven women reported that stress triggers or exacerbates their symptoms
- ◆ Eight women experienced improvement or complete resolution of symptoms with treatment with low-dose doxepin hydrochloride or amitriptyline hydrochloride
- ◆ One patient responded completely to treatment with sertraline and hydroxyzine hydrochloride but then experienced a relapse
- ◆ Hoss D, Segal S. Scalp dysesthesia. Arch Dermatol. 1998;134(3):327-30.



Glossodynia

(Burning mouth syndrome)



- ◆ Found in many menopausal women
- ◆ Oestrogen receptors have been detected in the oral mucosa and salivary glands.
- ◆ Yet, hormone replacement therapy use does not necessarily prevent or help women with oral symptoms
- ◆ Mock D, Chugh D. Burning mouth syndrome. *Int J Oral Sci.* 2010;2(1):1-4.
- ◆ "Unexplained somatic comorbidities in patients with burning mouth syndrome: a controlled clinical study"
- ◆ 112 BMS pat, 112 lichen, 102 controls. 83% of pat reported painful symptomatology in different bodily regions→BMS somatoform disorder rather than a neuropathic pain entity?
- ◆ Mignogna MD et al. *J Orofac Pain.*2011; 25:131-40,
- ◆ Treatment with serotonin and norepinephrin reuptake inhibitors



Vulvodynia

- ◆ Vulvodynia should be suspected in any female with a history of more than three months of pain at the introitus or vulva.
- ◆ Topical treatments include local gel anesthetics (such as lidocaine 2%) applied over the tender areas 5-10 minutes before sexual intercourse and estrogen cream (0.5 to 2 g) every other day intravaginally specially for perimenopausal women. Regional therapies are pudendal nerve block (usually with bupivacaine 0.5%), and pelvic floor muscle rehabilitation with or without biofeedback
- ◆ Psychological counseling and group support should be considered in all cases.

Edgardh K. Experiences with a special vulvar clinic in Oslo. Tidsskr Nor Laegeforen. 2005; 125(8):1026-7. National referral center

- ◆ Tricyclic antidepressants should be considered for the treatment of vulvodynia.
- ◆ Selective serotonin reuptake inhibitors and gabapentin should be considered for symptomatic relief of vulvodynia.
- ◆ Cognitive behavioral therapy should be used to decrease vulvar pain with intercourse

Reed BD. Vulvodynia: diagnosis and management. Am Fam Physician. 2006;73(7):1231-8.

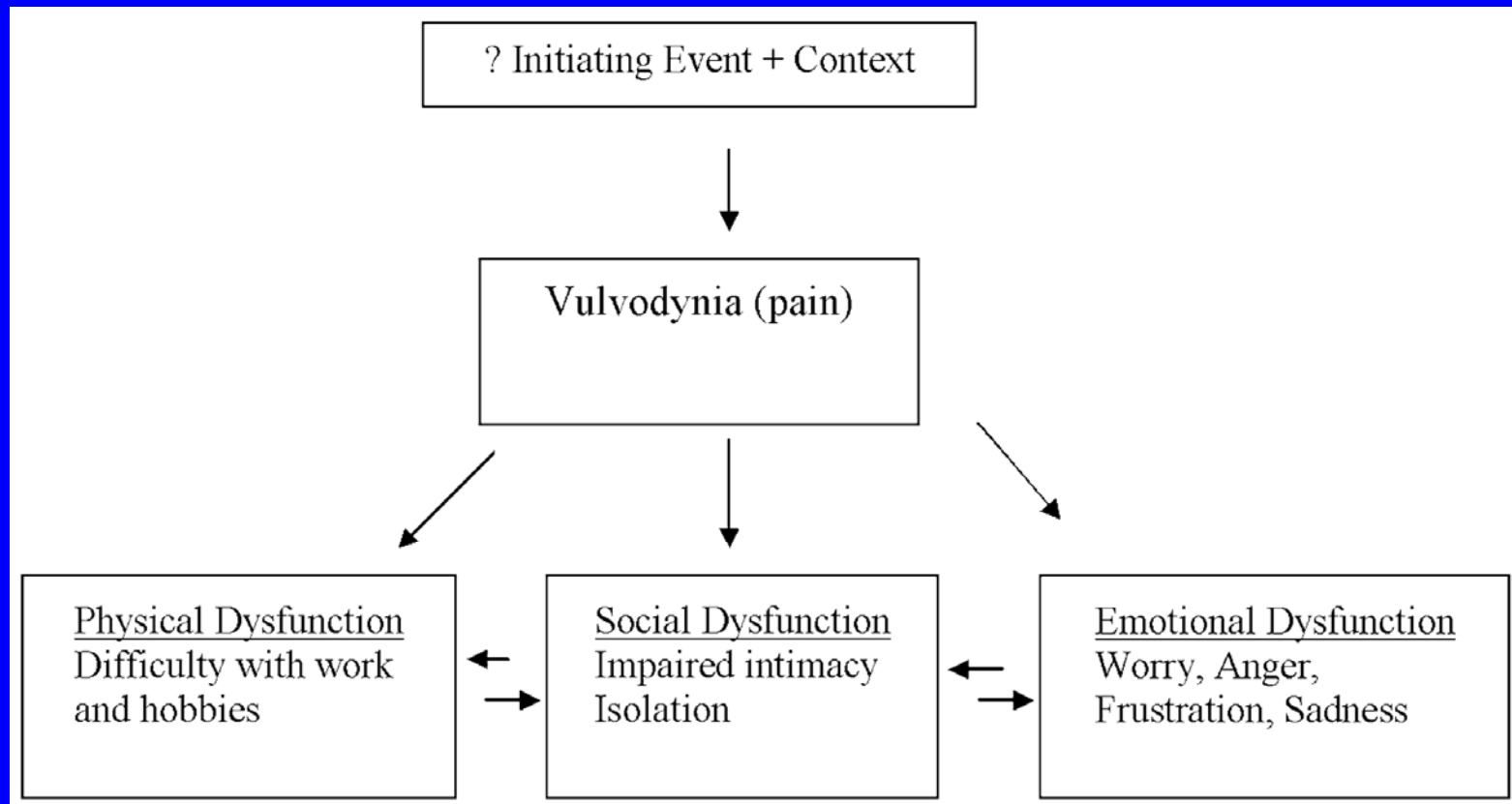


Dysaesthetic Peno/Scroto-dynia

- ◆ Pudendal neuralgia
- ◆ Pinprick sensation is decreased
- ◆ Elimination of irritants is recommended
- ◆ Tacrolimus treatment
- ◆ Tricyclic antidepressants and neuroleptics, chiefly gabapentin
- ◆ Physiotherapy and cognitive-behavioral therapy seem to be promising therapeutic tools
- ◆ Markos AR. The male genital skin burning syndrome (Dysaesthetic Peno/Scroto-dynia). *Int J STD AIDS*. 2002;13(4):271-2.



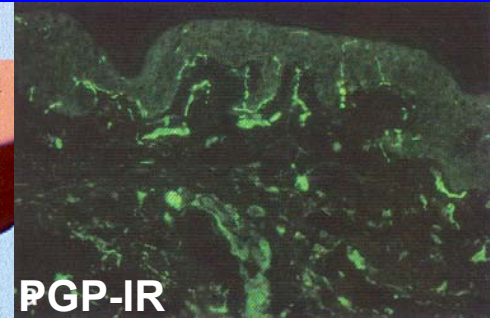
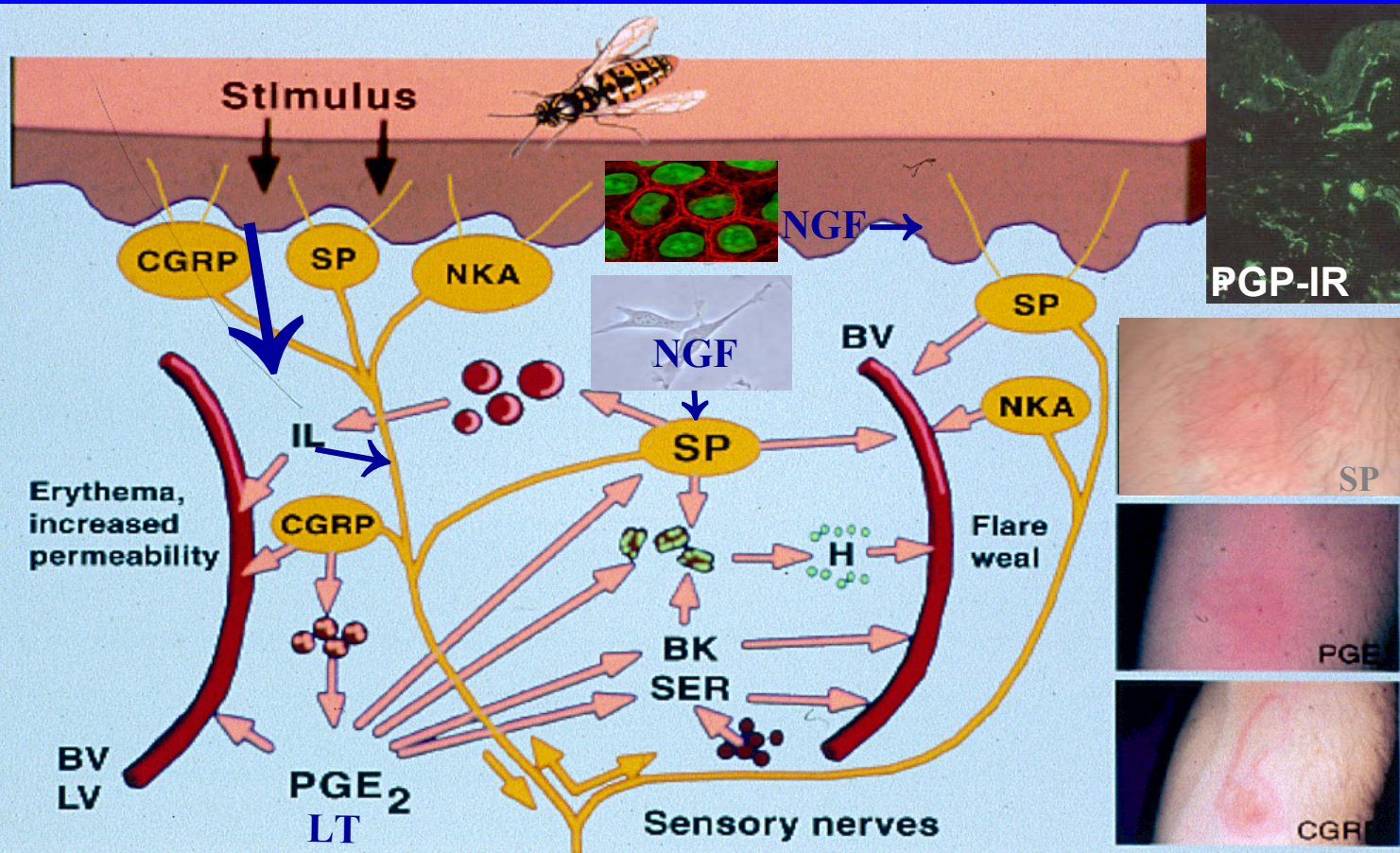
Effect of neuropathic itch on quality of life



- ◆ Ponte M et al. Effects of vulvodynia on quality of life. *J Am Acad Dermatol.* 2009; 60(1): 70–76.



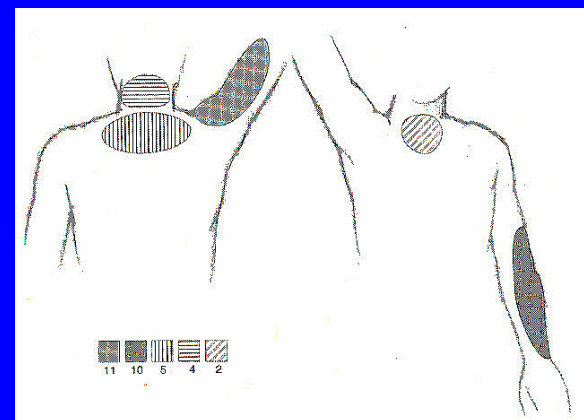
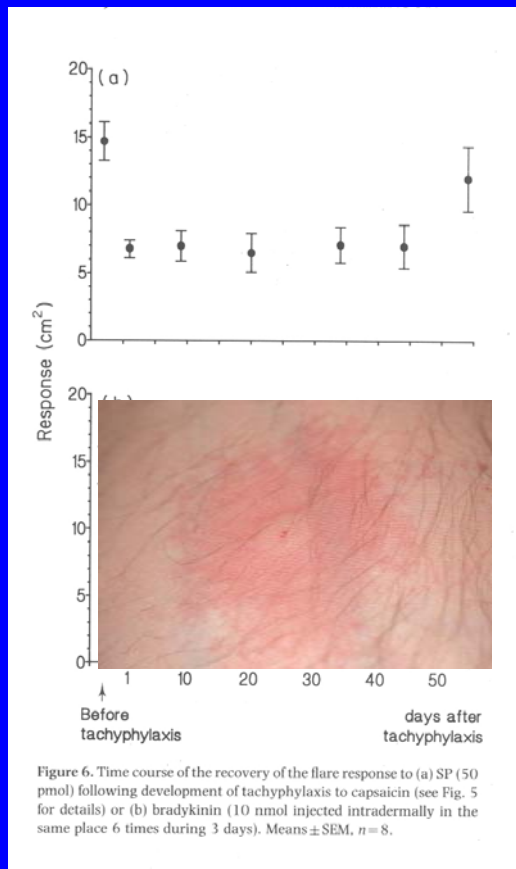
Peripheral mediators of itch and neurogenic inflammation



Mechano-insensitive C-fibers
receptor territories 85 mm diameter, conduction velocity 0,5 m/sec



Capsaicin treatment-tachyphylaxis



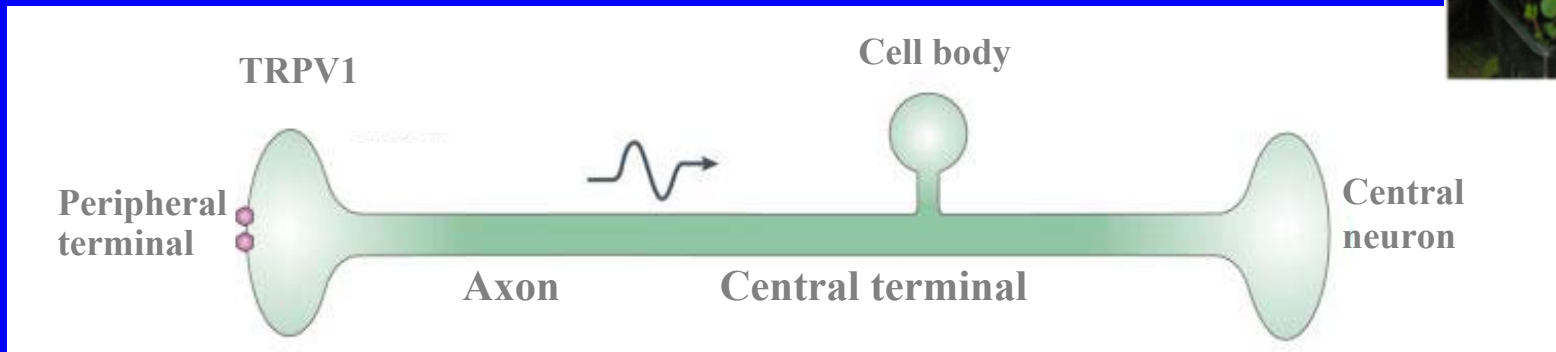
◆ Wallengren J, Klinker M. Successful treatment of notalgia paresthetica with topical capsaicin. Vehicle controlled, double-blind, cross-over study. *J Am Acad Dermatol* 1995; 32:287-289.



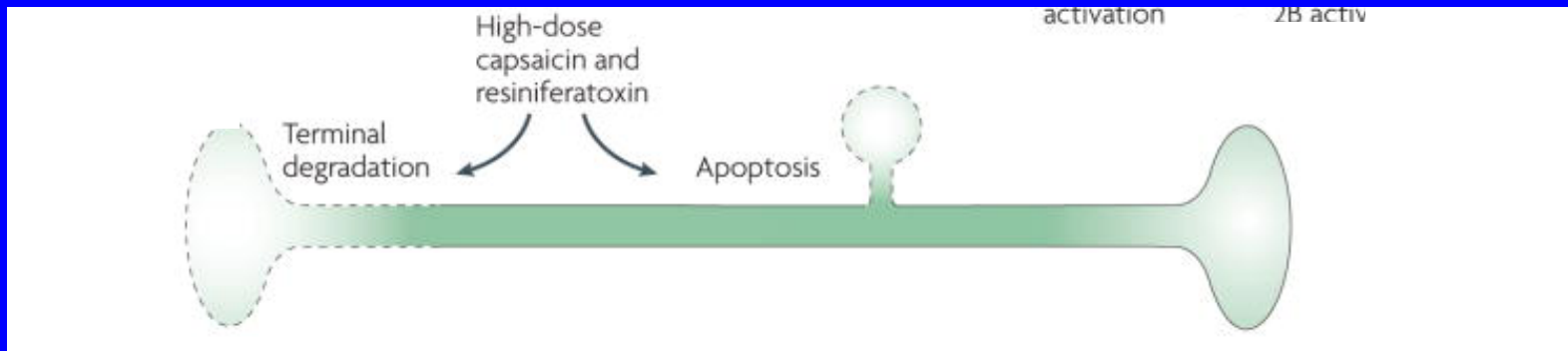
◆ Wallengren J, Håkanson R. Effects of capsaicin, bradykinin and prostaglandins in the human skin. *Br J Derm* 1992;126: 111-7



Transient receptor potential channels, “hot TRP receptors”

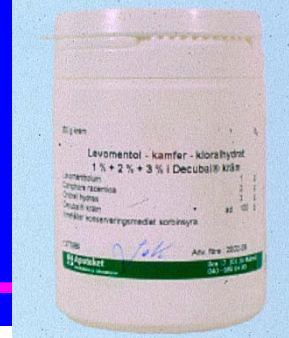


- ◆ Low dose treatment (0.025%) with TRPV1 agonist



- ◆ High dose treatment (8%) with TRPV1 agonist
- ◆ Pataoutian A et al. Transient receptor potential channels: targeting pain at the source. *Nat Rev Drug*, 2009;8(1):55-68.
- ◆ Metz M et al. Treatment of notalgia paresthetica with an 8% capsaicin patch. *Br J Dermatol* 2011 Dec

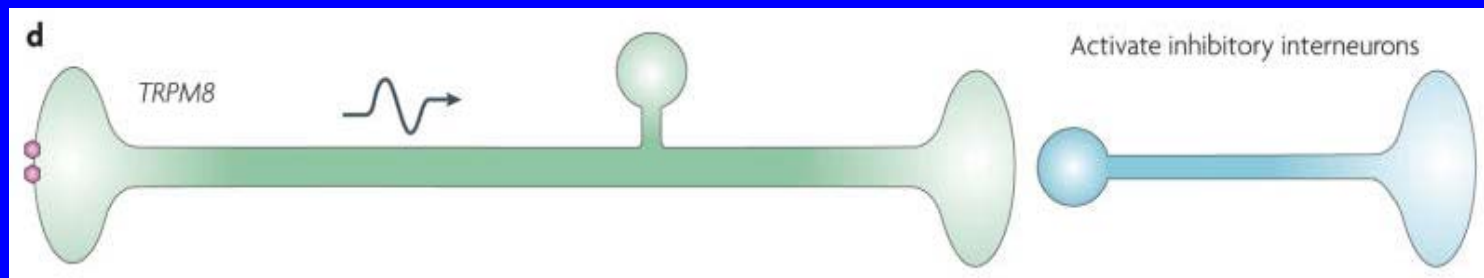




Hot and cold TRP receptor agonists



- ◆ Hot TRP receptor: TRPV3 –target of camphor, oregano



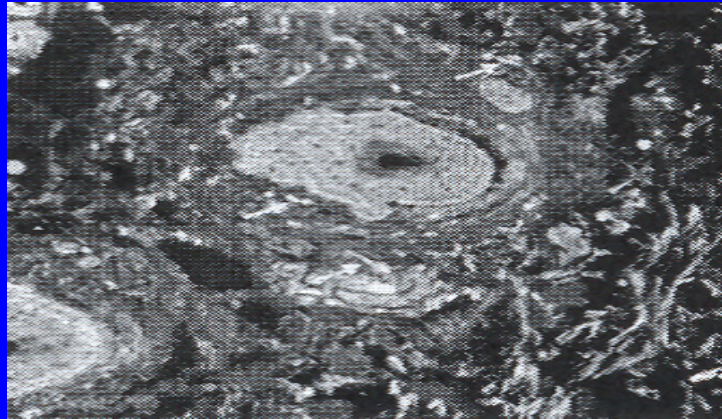
- ◆ Cold TRP receptor: TRP M8, target of menthol

Pataooutian A et al. Transient receptor potential channels: targeting pain at the source. *Nat Rev Drug*, 2009;8(1):55-68



Brachioradial pruritus – ice pack sign

Bernhard JD, Bordeaux JS. Medical pearl: the ice-pack sign in brachioradial pruritus. *J Am Acad Dermatol.* 2005; 52(6):1073.



- ◆ The number of hot-receptors, vanilloid-receptors (TRPV1) is reduced
- ◆ Cool receptor (TRPM8) belongs to the same family of TRP-channels, and is sensitive for menthol. It modulates activity in the sensory, thermo-sensitive nerve fibers that transmit itch
- ◆ A platform for stimulation of cool receptors with ice cubes?



Calcineurin-inhibitors and cannabinoid receptor agonists



- ◆ Tacrolimus and pimecrolimus anti-inflammatory potential of moderate steroids but better antipruritic potency
- ◆ Treatment twice daily
- ◆ Burning sensation on the application site, due to the release of neuropeptides, disappears after a few days (tachyphylaxis)

Antipruritic effect of pimecrolimus and tacrolimus. Ständer S, Luger TA. Hautarzt. 2003;54:413.



- ◆ Cannabinoid receptor agonists (Physiogel A.I., Stiefel Lab)
- ◆ Interfere with neurogenic inflammation
- ◆ Rukwied R et al. Cannabinoid receptor agonists attenuate capsaicin induced responses in human skin. Pain. 2003;102:283-8

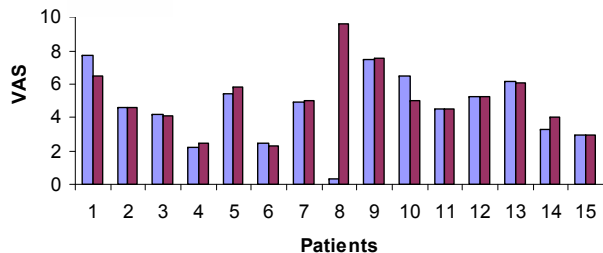


Substance P antagonist, aprepitant, and itch

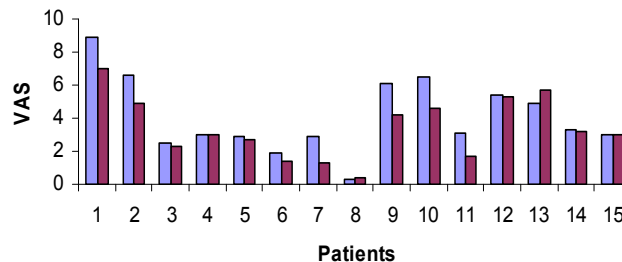
- ◆ A randomized, double blind, vehicle controlled, right-left study of in 13 patients (8 women, age range 33-82 years, median 57 y, 11 dermatitis, 4 PUO), treating 15 symmetrical skin regions

Ständer S et al. Targeting the neurokinin receptor 1 with aprepitant: a novel antipruritic strategy. PLoS One. 2010 4;5(6):e10968

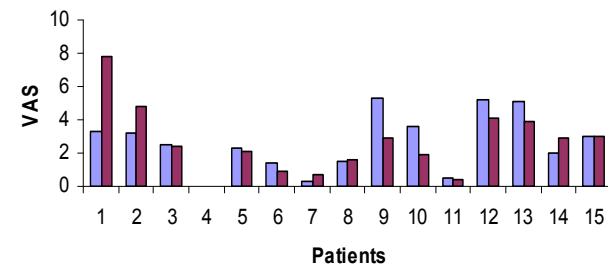
A. Rating of itch on the left vs the right side prior to treatment



B. The effect of 5% aprepitant vs of the vehicle alone 30 min after treatment



C. The effect of 5% aprepitant vs of the vehicle alone 2 hours after treatment



Wallengren J. Topical aprepitant in clinical and experimental pruritus. Arch Dermatol. Accepted



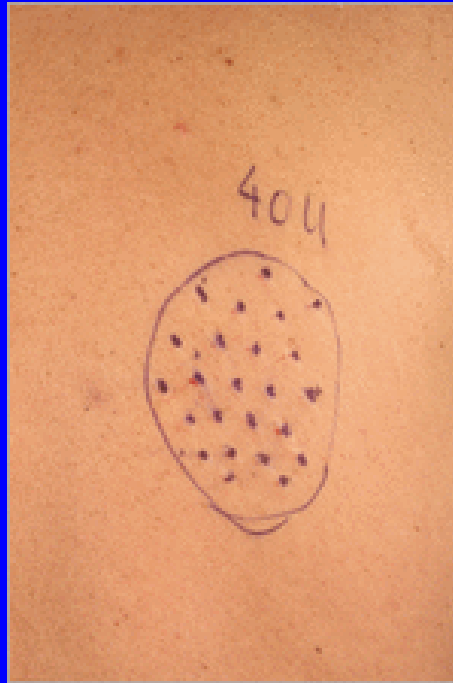
CFS - Cutaneous field stimulation



- ◆ Nilsson HJ, Levinsson A, Schouenborg J. Cutaneous field stimulation (CFS): a new powerful method to combat itch. *Pain* 1997; 71(1):49-55.
- ◆ Wallengren J, Sundler F. Cutaneous field stimulation (CFS) in treatment of severe localized itch. *Arch Dermatol.* 2001; 137: 1323-1325.
- ◆ Wallengren J. Cutaneous field stimulation of sensory nerve fibers reduces itch without affecting delayed cutaneous reactions. *Allergy* 2002; 57 (12): 1195-1199.
- ◆ Wallengren J, Moller K, Sundler F. Cutaneous field stimulation with moderate intensity current induces nerve proliferation in rat skin but has no effect on dorsal root ganglia. *Acta derm Venereol* 2005; 85 (4):324-8.

- ◆ Electric stimulation of C-fibers, can be adjusted by a knob, 9 V battery
- ◆ After 5 weeks of treatment patients with localized itching experienced a reduction of itch VAS 78% before treatment to 42%).
- ◆ The number of intraepithelial nerve fibers (PGP-IR), was reduced by 40% by the end of treatment

Botulinum toxin for neuropathic itch



- ◆ Intracutaneous injections of 0.8–1.4 U of BTX-A 1, 5 cm apart, without preservatives
- ◆ One treatment only in 6 patients. Totaly 18-100 U of BTX-A, depending on the size of the patch
- ◆ Improvement in VAS by 28%

- ◆ Wallengren J, Bartosik J. Botulinum toxin type A for neuropathic itch. *Br J Dermatol.* 2010;163(2):424-6.
- ◆ Weinfeld PK. Successful treatment of notalgia paresthetica with botulinum toxin type A. *Arch Dermatol*2007;143(8):980-2.
- ◆ Heckmann M, Heyer G et al. Botulinum toxin type A injection in the treatment of lichen simplex: an open pilot study. *J Am Acad Dermatol.* 2002 ;46(4):617-9



Acupuncture

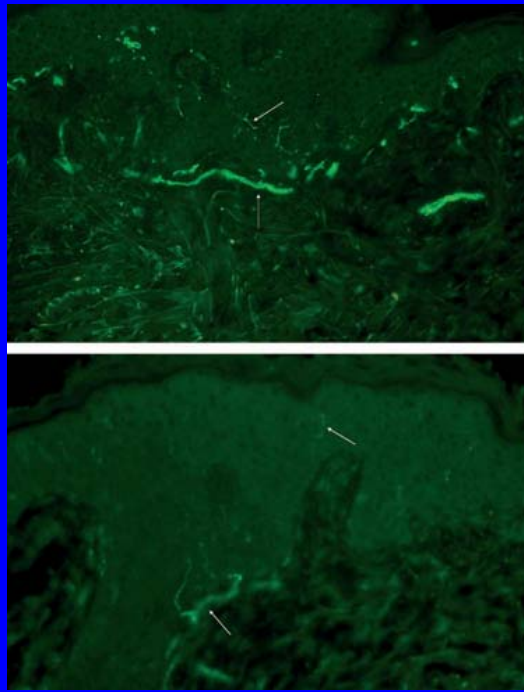


- ◆ Ten subjects were treated by inserting 10 acupuncture needles subcutaneously at the upper lateral aspect of one buttock
- ◆ The needles were stimulated (rotated to and fro) twice during the twice-weekly 25-min sessions over 5 weeks
- ◆ Skin biopsies, diameter 3 mm, were taken before and 3–6 days after local acupuncture.
- ◆ Carlsson CP, Wallengren J, Sundler F. Cutaneous innervation before and after one treatment period of acupuncture. *Br J Derm* 2006;155(5): 970-6
- ◆ Powell J, Wojnarowska F. Acupuncture for vulvodinia. *J R Soc Med.* 1999; 92(11):579-81.



Cutaneous innervation before and after one treatment period of acupuncture

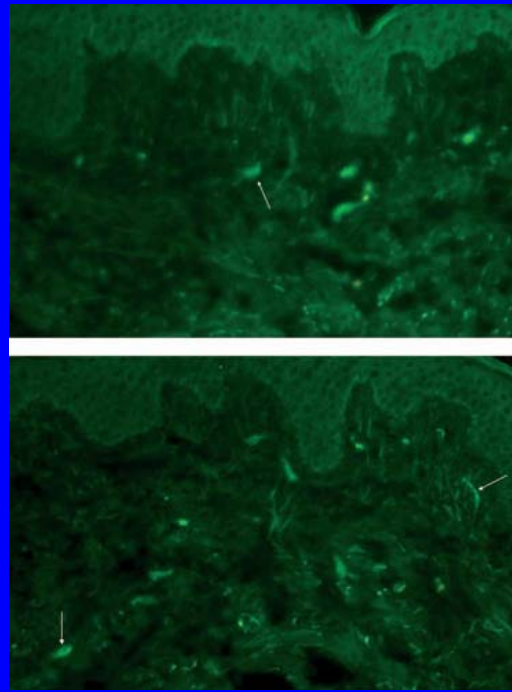
Immunoreactive nerve fibers before and after acupuncture



◆ PGP-IR

249.8 ± 16.7 vs

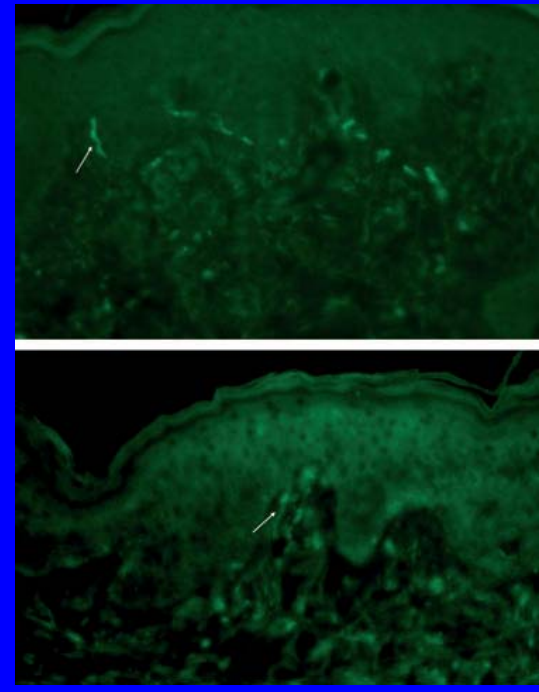
211.8 ± 12.0 ($p = 0.03$)



◆ CGRP -IR

36.0 ± 3.3 vs

21.3 ± 4.0 ($p = 0.05$)



◆ TRPV1-IR

33.5 ± 4.6 vs

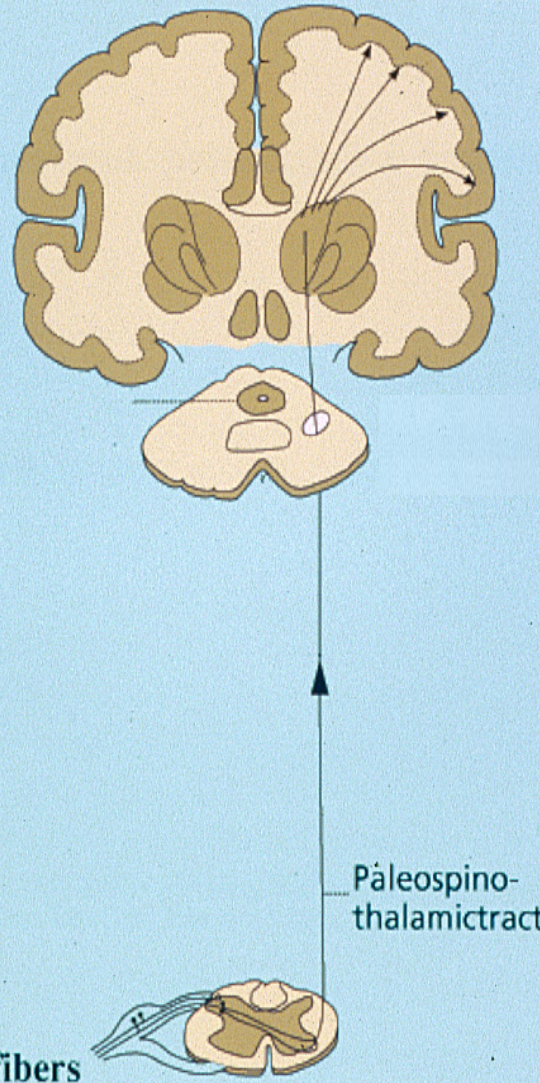
43.0 ± 4.4 ($p = 0.09$)



Peripheral and central transmission of itch

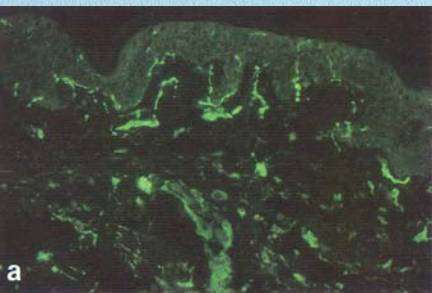
Peripheral neurotransmitters

Ach
CGRP
GA
GABA
NA
NKA
NO
NPY
PACAP
SP
VIP



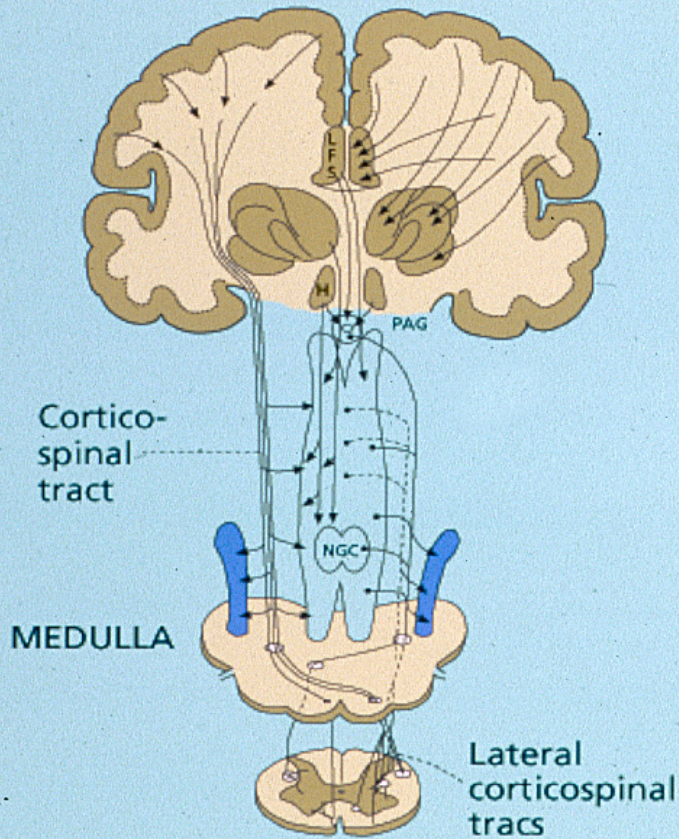
Central neurotransmitters

Ach
CGRP
Dopamine
Dynorphin
Endorphin
Enkefalin
GABA
MSH
NA
NO
NPY
Oxytocin
PACAP
Serotonin
Somatostatin
SP
VIP
Histamine



Central transmission of itch

Messengers of mood



Descending pain/itch control system

From Bonica JJ ed. The management of pain 1990.

Depression

GABA

Dopamine

Serotonin

NPY

SP

Opioids, (μ -, κ -receptors)

Cutaneous delusions

Opioids (μ -, κ -receptors)

Dopamine

NA

Serotonin

Hyperactivity disorders

NA

Dopamine

Histamine (H1, H4 receptors)



Central inhibition of itch



- ◆ *Naltrexon,*

Mu-opioid receptor antagonist is effective in pruritus of skin disease, cholestasis and renal failure

Twycross R, Greaves MW et al. Itch: scratching more than the surface. QJM. 2003;96:7-26.

- ◆ *Gabapentin,*

Anticonvulsant which resembles GABA (γ -amino- butyric acid). Has been used in itch due to cholestasis, renal failure and PUO

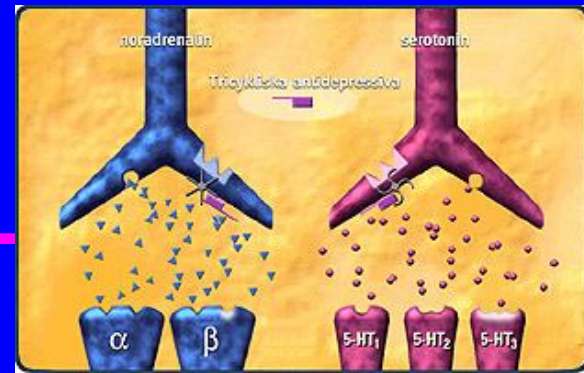
Bergasa NV et al. Gabapentin in patients with the pruritus of cholestasis: a double-blind, randomized, placebo-controlled trial. Hepatology. 2006; 44: 1317-23.

- ◆ Its use for neuropathic pain has become widespread because it is generally well-tolerated, easily titrated, has few drug interactions, and does not require laboratory monitoring.

- ◆ Ben-David B, Friedman M. Gabapentin therapy for vulvodynia. Anesth Analg. 1999;89(6):1459-60.



Antidepressants



- ◆ *Mirtazapine,*

NA- and serotonin-antagonist with H1 activity
Successfully used in patients with malignant cholestasis, lymphoma and renal failure

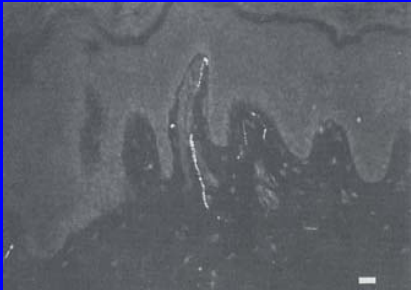
- ◆ *Paroxetine,*

Selective serotonin re-uptake inhibitor (SSRI).
Successfully used in patients with paramalignant itch (ca pulm, ca colon and ca prostatae) and morphin-induced itch

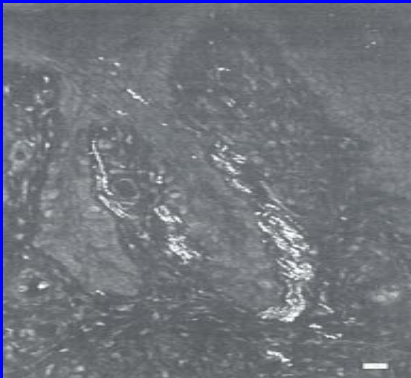
Twycross R, Greaves MW et al. Itch: scratching more than the surface. QJM. 2003;96(1):7-26.



Generalized neuropathic itch in chronic prurigo



- ◆ Chronic prurigo: thick nerve fiber bundles (Johnston, 1899) and infiltrate of mast cells and eosinophils
- ◆ Proliferation of nerve fibers



- ◆ Vaalasti A et al. Br J Dermatol. 1989; 20: 619-23. Calcitonin gene-related peptide immunoreactivity in prurigo nodularis: a comparative study with neurodermatitis circumscripta.



Prurigo and emotional factors



- ◆ 50% of the patients with prurigo were treated for depression, anxiety or some other psychological disorder
- ◆ 72% of the patients felt that psychosocial problems were of relevance for prurigo

Rowland Payne et al. Br J Derm 1985; 113: 431

- ◆ Neurotransmitters of mood such as dopamine, serotonin or opioid peptides modulate sensory perception



Psychopharmacologic intervention



- ◆ Depression, anxiety or other psychological disorders may be associated with prurigo
- ◆ *SSRI antidepressant* (serotonin re-uptake inhibitor) in depression or in compulsive behaviour with scratching
- ◆ *Pimozide* in anxiety (opioid pathways associated with itch)
- ◆ *Chlordiazepoxide* or *diazepam* - tranquillisers



Localized itch due to a cerebral lesion

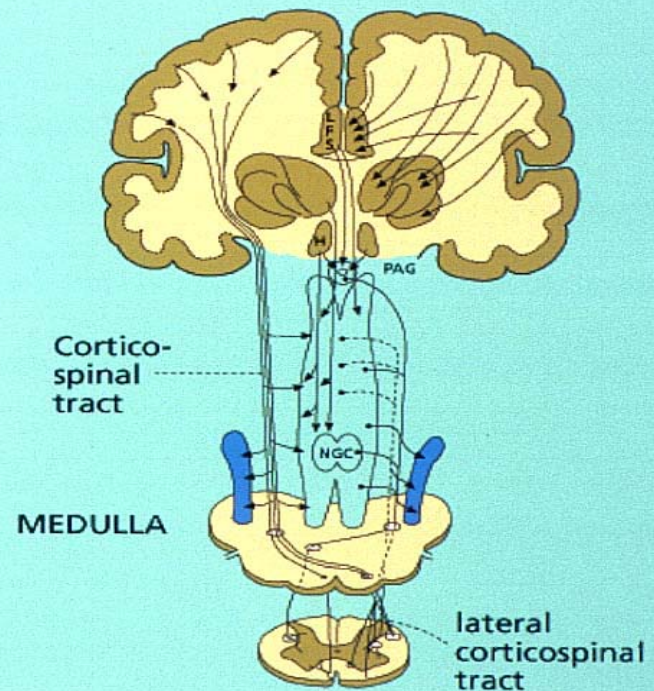
Central neuropathic itch

Itch in nostrils due to tumor cerebri

Unilateral pruritus after a stroke
in the distribution of the:

1. Middle cerebral artery (5 pat)
2. Capsula interna and thalamus (6 pat)
3. Parietal lobe (1 pat)

Unilateral pruritus after a stroke

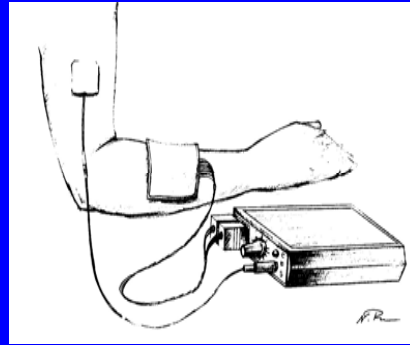
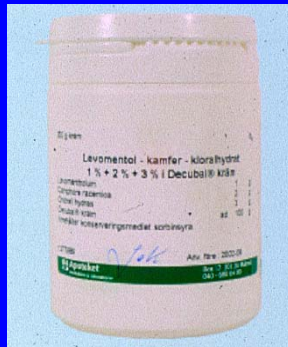


Descending pain / itch control system

From Bonica JJ ed. The management of pain. 1990.



Conclusion



- ◆ The approach to the patient begins with acknowledging that the symptom is well described, searching for a secondary cause, and performing a careful psychologic assessment. Treatment is empirical and patients can often be helped with medications used to treat neuropathic pain, all the while providing psychologic support and exercising caution toward invasive and irreversible therapeutic procedures
- ◆ Wesselmann U, Reich SG. The dynias. *Semi Neurol.* 1996;16(1):63-74.

