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This newsletter is quarterly and contains references from medical journal articles published between June and August of 2001. Please direct any comments regarding this newsletter to chris@nva.org.

The expression of cyclooxygenase 2 and inducible nitric oxide synthase indicates no active inflammation in vulvar vestibulitis

Bohm-Starke N, Falconer C, Rylander E, Hilliges M

Acta Obstet Gynecol Scand 2001 Jul;80(7):638-44

BACKGROUND: Although women with vulvar vestibulitis syndrome have principal symptoms of inflammation such as local erythema and pain in the mucosa around the vaginal introitus, it is not clear if vestibulitis is an inflammatory condition. Cyclooxygenase 2 and inducible nitric oxide synthase are known to be upregulated during inflammation. The aim of the present study was to analyze the expression of these enzymes in the vestibular mucosa in order to evaluate the inflammatory activity in the tissue. METHODS: Ten women fulfilling Friedrich's criteria of vulvar vestibulitis syndrome and ten control subjects were included in the study. Punch biopsies were obtained from the vestibular mucosa for analysis of cyclooxygenase 2 and inducible nitric oxide synthase, using indirect immunohistochemistry and Western dot-blot analyses. RESULTS: Both methods used showed low expression of cyclooxygenase 2 and inducible nitric oxide synthase in the vestibular mucosa of all women. There was no difference observed between the groups. CONCLUSIONS: There is a low expression of the inflammatory markers cyclooxygenase 2 and inducible nitric oxide synthase in the vestibular mucosa of women with vulvar vestibulitis syndrome as well as in healthy control subjects. The results indicate no active inflammation present and imply that topical corticosteroids in the treatment of vulvar vestibulitis are unfounded.

Vulvar vestibulitis syndrome: reliability of diagnosis and evaluation of current diagnostic criteria

Bergeron S, Binik YM, Khalife S, Pagidas K, Glazer HI

Obstet Gynecol 2001 Jul;98(1):45-51

Objective: To assess the reliability of the diagnosis of vulvar vestibulitis as defined by Friedrich and to evaluate the usefulness of Friedrich's criteria in the diagnostic process. Methods: In a university hospital, 146 women with dyspareunia had two sets of gynecologic examinations involving vulvar pain ratings, took part in structured interviews, and completed the McGill-Melzack Pain Questionnaire. Results: Kappa values for the vulvar vestibulitis diagnosis ranged from 0.66 to 0.68 for inter-rater agreement and from 0.49 to 0.54 for test-retest reliability. Mean vestibular pain ratings ranged from 2.45 at the 12 o'clock site to 7.58 at the 9-12 o'clock site; ratings for all sites correlated significantly between gynecologists. Pain in the labia majora and labia minora was minimal for both sets of examinations, with mean participant pain ratings ranging from 0 to 1.49. Gynecologists' erythema ratings did not correlate significantly with respect to either inter-rater agreement or test-retest reliability. Of Friedrich's three diagnostic criteria, only tenderness to pressure within the vulvar vestibule differentiated dyspareunia patients with and without vulvar vestibulitis. In reference to their coital pain, 88.1% of women with vulvar vestibulitis chose adjectives from the McGill-Melzack Pain Questionnaire describing a thermal quality, and 86.6% chose adjectives describing an incisive pressure sensation. Conclusion: Vulvar vestibulitis can be reliably diagnosed in women with dyspareunia. Pain is limited to the vulvar vestibule and can be rated and described in a consistent fashion by these women. Erythema does not appear to be a useful diagnostic criterion.

Vulvodynia after CO2 laser treatment of the female genital mucosa

Tschanz C, Salomon D, Skaria A, Masouye I, Vecchietti GL, Harms M

Dermatology 2001;202(4):371-2

We have observed 3 cases of vulvodynia after CO2 laser (pulse or scan) treatment of condylomata acuminata (n = 1) or bowenoid papulosis (n = 2) of the female genital mucosa. Laser treatment was associated with a considerable delay in healing (3-4 months) and chronic pain. The histology of the treated areas showed a scar tissue and severe mucosal atrophy. The occurrence of painful scars following CO2 laser treatment could be related to an inadequate laser technique considering the morphology of the vagina.

Psychosexual aspects of vulvar vestibulitis

Sackett S, Gates E, Heckman-Stone C, Kobus AM, Galask R

J Reprod Med 2001 Jun;46(6):593-8

OBJECTIVE: To explore the psychological, interpersonal and sexual correlates of vulvar vestibulitis via qualitative and quantitative analysis. STUDY DESIGN: Sixty-nine women diagnosed with vestibulitis were recruited from a vulvar/vaginal disease clinic to complete a comprehensive quantitative and qualitative questionnaire designed to assess general health concerns, mental health, sexual functioning and interpersonal relationships. RESULTS: The majority of participants reported drastic changes in sexuality associated with the onset of vestibulitis. Upon developing vestibulitis, 88% reported decreased interest in sexual activity, 87% indicated that they were less

willing to participate in sexual activity, and 94% maintained that they were less able to participate in sexual activity. High levels of frustration and symptoms of depression also were frequently reported. CONCLUSION: Vulvar vestibulitis is associated with significant changes in sexuality, intimate relationships and psychological well-being. When treating women with vestibulitis, medical professionals should consider the psychological and sexual aspects of the disease in addition to physical concerns.

Vestibulodynia: tracing and treating vulvar pain

Stewart EG

OBG Management, July 2001

<http://www.obgynlinx.com/thearts.cfm?readurl=&artid=184023&specid=5>

[Vulvodynia: a problem of definition]

[Article in French]

Moyal Barraco M

Ann Dermatol Venereol 2001 Jun-Jul;128(6-7):763; discussion 764-5

[Vulvar vestibulitis is not necessarily confusing]

[Article in Swedish]

Bohm-Starke N, Rylander E

Lakartidningen 2001 Feb 14;98(7):718

Gynecologic presentation of interstitial cystitis as detected by intravesical potassium sensitivity

Parsons CL, Bullen M, Kahn BS, Stanford EJ, Willems JJ

Obstet Gynecol 2001 Jul;98(1):127-32

Objective: To document the initial clinical diagnoses, determine the prevalence of urinary symptoms, and test for intravesical potassium sensitivity in gynecologic patients with chronic pelvic pain. Methods: Gynecologists at three United States medical centers administered the Potassium Sensitivity Test to consecutive unselected pelvic pain patients. Before testing, each patient was given an initial clinical diagnosis based on the patient's chief symptomatic complaint(s) and surveyed for urologic symptoms. Results: Of 134 patients, 114 (85%) had positive potassium sensitivity. Positive potassium sensitivity rates were similar across all three sites and all clinical diagnoses including endometriosis, vulvodynia

(vulvar vestibulitis), and pelvic pain. A total of 75% of the subjects reported urologic symptoms, but only 2.9% received an initial diagnosis of interstitial cystitis. Conclusion: A significant majority of gynecologic patients presenting with pelvic pain have a positive Potassium Sensitivity Test, indicating their pain may have a bladder component (interstitial cystitis). Interstitial cystitis deserves greater consideration in the differential diagnosis of chronic pelvic pain.

The classic approach to diagnosis of vulvovaginitis: a critical analysis

Bornstein J, Lakovsky Y, Lavi I, Bar-Am A, Abramovici H

Infect Dis Obstet Gynecol 2001;9(2):105-11

OBJECTIVE: To correlate the symptoms, signs and clinical diagnosis in women with vaginal discharge, based on the combined weight of the character of the vaginal discharge and bedside tests, with the laboratory diagnosis. METHODS: Women presenting consecutively to the women's health center with vaginal discharge were interviewed and examined for assessment of the quantity and color of the discharge. One drop of the material was then examined for pH and the whiff test was done; a wet mount in saline and in 10% KOH was examined microscopically. The clinical diagnosis was based on the results of these assessments. Gram stain and cultures of the discharge were sent to the microbiology laboratory. RESULTS: One hundred and fifty-three women with vaginal discharge with a clinical diagnosis of vulvovaginitis participated in the study. Fifty-five (35.9%) had normal flora and the other 98 (64.1%) had true infectious vulvovaginitis (kappa agreement = 18%). According to the laboratory, the principal infectious micro-organism causing the vulvovaginitis was Candida species. Candida infection was associated with pH levels of less than 4.5 ($p < 0.0001$, odds ratio = 4.74, 95% confidence interval: 2.35-9.5, positive predictive value 68.4%). The whiff test was positive in only a small percentage of bacterial vaginosis (BV) ($p =$ not significant (NS)). Clue cells were documented in 53.3% of patients with a laboratory diagnosis of BV ($p < 0.02$, positive predictive value 26.7%). CONCLUSIONS: The current approach to the diagnosis of vulvovaginitis should be further studied. The classical and time-consuming assessments were shown not to be reliable diagnostic measures.

Treatment of complicated Candida vaginitis: Comparison of single and equential doses of fluconazole

Sobel JD, Kapernick PS, Zervos M, Reed BD, Hooton T, Soper D, Nyirjesy P, Heine MW, Willems J, Panzer H, Wittes H

Am J Obstet Gynecol 2001 Aug;185(2 Pt 1):363-369

OBJECTIVE: An attempt was made to validate recent recommendations that women with complicated Candida vaginitis (severe or recurrent, non-albicans Candida spp or abnormal host) require longer-duration antifungal therapy to achieve clinical cure and mycologic eradication. Study Design: A prospective, multicenter, randomized, double-blind study was performed comparing a single dose of 150 mg of fluconazole with 2 sequential 150-mg doses of fluconazole given 3 days apart. RESULTS: Five hundred fifty-six women with severe or

recurrent *Candida* vaginitis were enrolled, and 398 had at least one postbaseline evaluation (intent to treat) and of these 309 were fully evaluable (efficacy-valid). At baseline, 92% of vaginal isolates were *Candida albicans*. The 2-dose fluconazole regimen achieved significantly higher clinical cure rates in women with severe vaginitis when evaluated on day 14 ($P = .015$) and higher clinical and mycologic responses persisted at day 35. Women with recurrent but not severe vaginitis did not benefit clinically short term by the additional fluconazole dose. Multivariate logistic regression analysis showed that being infected with non-*albicans* *Candida* predicted significantly reduced clinical and mycologic response regardless of duration of therapy. Fluconazole therapy was well tolerated and free of serious adverse effects. CONCLUSION: Treatment of *Candida* vaginitis requires individualization, and women with severe *Candida* vaginitis achieve superior clinical and mycologic eradication with a 2-dose fluconazole regimen.

The community prevalence of chronic pelvic pain in women and associated illness behaviour

Zondervan KT, Yudkin PL, Vessey MP, Jenkinson CP, Dawes MG, Barlow DH, Kennedy SH

Br J Gen Pract 2001 Jul;51(468):541-7

BACKGROUND: Chronic pelvic pain has often been described as a major women's health issue, but no information exists on the extent of the problem in the United Kingdom. AIM: To investigate the community prevalence of chronic pelvic pain and its effect on the lives of consulting and non-consulting women. DESIGN OF STUDY: Postal questionnaire survey. SETTING: Women aged 18 to 49 ($n = 3916$) randomly selected from the Oxfordshire Health Authority Register. METHOD: The questionnaire response rate (adjusted for non-deliveries) was 74% (2304/3106). Chronic pelvic pain was defined as recurrent or constant pelvic pain of at least six months' duration, unrelated to periods, intercourse, or pregnancy. Case subgroups comprised recent consulters, past consulters, and non-consulters. Women who reported dysmenorrhoea alone formed a comparison group. RESULTS: The three-month prevalence of chronic pelvic pain was 24.0% (95% CI = 22.1% to 25.8%). One-third of women reported pain that started more than five years ago. Recent consulters (32% of cases) were most affected by their symptoms in terms of pain severity, use of health care, physical and mental health scores, sleep quality, and pain-related absence from work. Non-consulters (41% of cases) did not differ from women with dysmenorrhoea in terms of symptom-related impairment. Irrespective of consulting behaviour, a high rate of symptom-related anxiety was found in women with chronic pelvic pain (31%) compared with women with dysmenorrhoea (7%). CONCLUSIONS: This study showed a high community prevalence of chronic pelvic pain in women of reproductive age. Cases varied substantially in the degree to which they were affected by their symptoms. The high symptom-related anxiety in these women emphasises the need for more information about chronic pelvic pain and its possible causes.

Menopause and the skin

Wines N, Willstead E

Women live one-third of their lives in the post-menopausal state. Significant hormonal alterations occur at the time of menopause, leading to a range of physiological disorders affecting multiple organ systems in the body. The effects of menopause on the skin have been underresearched. Many skin changes occur at the time of menopause and the cutaneous effects of hormone replacement therapy are significant. Menopausal changes in hormones may alter the biomechanical properties of the skin and certain disorders are more common in menopausal women, such as lichen sclerosus, atrophic vulvovaginitis, flushing and dysaesthetic vulvodinia. Hair and oral changes may also be associated. As the average life expectancy increases, dermatologists need to be familiar with skin diseases affecting women in this age group.

Blockade of the Superior Hypogastric Plexus Block for Visceral Pelvic Pain

Bosscher H

Pain Practice 1 (2), 162-170

Visceral pelvic pain is a common problem with variable etiology. The sympathetic nervous system plays an important role in the transmission of visceral pain independent of its etiology. Five major pathways by which pelvic pain is transmitted can be identified. One of them, the superior hypogastric plexus, an extension of the preaortic plexus, is easily assessable to blockade by local anesthetics and neurolytic agents. Several techniques have been described. Long-lasting pain relief with this procedure has been achieved in patients with pelvic cancer pain. However, there is a discrepancy between diagnostic and therapeutic blockade in patients with nonmalignant pain. Because a diagnostic blockade can give significant pain relief in a large variety of patients, it is worthwhile to investigate new methods that provide lasting neural blockade of the superior hypogastric plexus and long-lasting relief of this devastating condition.

Clinical neurophysiology and electrodiagnostic testing of the pelvic floor

Olsen AL, Rao SS

Gastroenterol Clin North Am 2001 Mar;30(1):33-54, v-vi

This article summarizes our current understanding of the neuroanatomy and neurophysiology of the pelvic floor. The electrodiagnostic evaluation of the pelvic floor muscles and external anal sphincter, including pudendal nerve conduction studies, sacral reflexes, and needle EMG is presented. The discussion reviews the test methodology, the strengths and limitations of each test, and their clinical utility. The authors have tried to critically review the objective evidence to support the use of electrodiagnostic tests in the evaluation and management of pelvic floor disorders. The reader will have a better understanding of the rationale, methodology, clinical utility, and potential pitfalls for each of the commonly used neurophysiological tests of the pelvic floor.

Pharmacology of oral combination analgesics: rational therapy for pain

Raffa RB

Journal of Clinical Pharmacy & Therapeutics 26 (4), 257-264

No single analgesic agent is perfect and no single analgesic can treat all types of pain. Yet each agent has distinct advantages and disadvantages compared to the others. Hence, clinical outcomes might be improved under certain conditions with the use of a combination of analgesics, rather than reliance on a single agent. A combination is most effective when the individual agents act through different analgesic mechanisms and act synergistically. By activating multiple pain-inhibitory pathways, combination analgesics can provide more effective pain relief for a broader spectrum of pain, and might also reduce adverse drug reactions. This overview highlights the therapeutic potential of combining analgesic medications with different mechanisms of action, particularly a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen with an opioid or tramadol.

Vagus nerve stimulation - a new option for the treatment of chronic pain syndromes

Kirchner A, Birklein F, Stefan H, Handwerker HO

Der Schmerz Volume 15 Issue 4 (2001) pp 272-277

Electrical stimulation of the vagal nerve (VNS) has become an established method for treating medically refractory epilepsies. From animal experiments it is well known that depending on the stimulation intensity VNS can elicit both inhibition and facilitation of nociception. Recent physiologic investigations demonstrated a similar influence of VNS on pain perception in patients treated by chronic VNS. However, in humans, a more marked effect was shown for the pain inhibition which is probably mediated by neurobiochemical mechanisms. These findings are discussed in consideration of the physiologic mechanisms underlying the modulation of pain and seizures by VNS known from animal studies. First reports of attenuation of chronic pain by VNS indicate that the method might be an option for pain treatment in the future.

Cortical representation of the sensory dimension of pain

Hofbauer RK, Rainville P, Duncan GH, Bushnell MC

J Neurophysiol, 86: 402-411, 2001

It is well accepted that pain is a multidimensional experience, but little is known of how the brain represents these dimensions. We used positron emission tomography (PET) to indirectly measure pain-evoked cerebral activity before and after hypnotic suggestions were given to modulate the perceived intensity of a painful stimulus. These techniques were similar to those of a previous study in which we gave suggestions to modulate the perceived unpleasantness of a noxious stimulus. Ten volunteers were scanned while tonic warm and

noxious heat stimuli were presented to the hand during four experimental conditions: alert control, hypnosis control, hypnotic suggestions for increased-pain intensity and hypnotic suggestions for decreased-pain intensity. As shown in previous brain imaging studies, noxious thermal stimuli presented during the alert and hypnosis-control conditions reliably activated contralateral structures, including primary somatosensory cortex (S1), secondary somatosensory cortex (S2), anterior cingulate cortex, and insular cortex. Hypnotic modulation of the intensity of the pain sensation led to significant changes in pain-evoked activity within S1 in contrast to our previous study in which specific modulation of pain unpleasantness (affect), independent of pain intensity, produced specific changes within the ACC. This double dissociation of cortical modulation indicates a relative specialization of the sensory and the classical limbic cortical areas in the processing of the sensory and affective dimensions of pain.

Nociceptive visceral stimulation modulates the activity of cerebellar Purkinje cells

Saab CY, Willis WD

Exp Brain Res 2001 Sep;140(1):122-6

The cerebellum is a system with various input and output functions that influence motor, sensory, cognitive, and other processes. In a previous study, we showed that cerebellar cortical stimulation increases spinal neuronal responses to visceral noxious stimulation by colorectal distension (CRD). However, the neuronal network underlying the cerebellar modulation of nociceptive phenomena is largely unknown. Purkinje cells of the cerebellar cortex receive ascending and descending inputs and exert a major inhibitory control over neurons in the underlying cerebellar nuclei that constitute the cerebellar output. Therefore, in this study, we tested the effect of CRD and other somatic stimuli on the firing rate of Purkinje cells using in vivo extracellular recording techniques. The results suggest that Purkinje cells respond to nociceptive visceral and somatic stimulation in the form of early and delayed changes in activity. Based on these and previous findings, we propose a negative feedback circuitry involving the cerebellum for the modulation of peripheral nociceptive events.

Spinal NK1 receptor is upregulated after chronic bladder irritation

Ishigooka M, Zermann D, Doggweiler R, Schmidt RA, Hashimoto T, Nakada T

Pain 2001 Jul;93(1):43-50

It has been suggested that there is a significant upregulation of the NK1 receptor (NK1R) on neurons in the dorsal spinal cord after long-term somatic inflammation. This upregulation appears to play a significant role in central sensitization in chronic pain states. However, it is not clear whether such a change is also observed after chronic visceral (bladder) inflammation. Changes in NK1R immunoreactivity after chronic bladder irritation were investigated in order to evaluate the existence of hypersensitive states in the spinal cord after chronic bladder irritation. Experiments were performed on a total of 12 adult female Sprague-Dawley rats. In six animals, cyclophosphamide (CPA) was administered intraperitoneally for 2 weeks.

Another six animals were given intraperitoneal saline injections and served as the control group. After these treatments, immunohistochemical staining for NK1Rs and substance P in rat lumbosacral spinal cord was performed. In CPA-treated animals, NK1R-positive areas and staining intensity within the dorsal spinal cord were significantly increased in the L5 to S2 spinal cord areas, especially in the L6 and S1 segments. In the L6 spinal segment, CPA-treatment enhanced NK1R immunostaining in the medial and the lateral dorsal horn, as well as in the lateral laminae including the sacral parasympathetic nucleus to a lesser extent. In CPA-treated animals, substance P staining intensity increased in the same regions in which NK1R immunoreactivity was increased. This finding probably implies the upregulation of spinal NK1R and the occurrence of central sensitization within the spinal cord after chronic visceral inflammation.

Gabapentin actions on N-methyl-D-aspartate receptor channels are protein kinase C-dependent.

Gu Y, Huang LM

Pain 2001 Jul;93(1):85-92

Gabapentin (Neurontin((R))) (GBP) is a widely prescribed analgesic used in treating pain patients with peripheral nerve injuries, diabetic neuropathy and cancer. To understand the mechanism of its action, we used the whole-cell patch recording technique to study the effects of GBP on N-methyl-D-aspartate (NMDA)-evoked currents in single dorsal horn neurons isolated from normal rats and from rats with inflammation induced by the injection of complete Freund adjuvant (CFA) to the hindpaw. We found that GBP enhanced NMDA currents in normal neurons only when protein kinase C (PKC) was added to these cells. The enhancement resulted from an increase in the affinity of glycine for NMDA receptors by GBP. In contrast, in neurons isolated from CFA-treated rats, GBP enhanced NMDA responses without any PKC treatment. Since endogenous PKC in inflamed tissue is elevated, these results suggest that GBP exerts its effects only on those cells affected by inflammatory injuries. Thus, the effects of GBP on NMDA receptors are plastic; they depend on the phosphorylation states of cells or receptors. These observations point to a new strategy for drug design. A chemical whose action depends on the state of cells would maximize its effectiveness while keeping its side-effects to a minimum.

NF-kappaB decoy suppresses cytokine expression and thermal hyperalgesia in a rat neuropathic pain model

Sakaue G, Shimaoka M, Fukuoka T, Hiroi T, Inoue T, Hashimoto N, Sakaguchi T, Sawa Y, Morishita R, Kiyono H, Noguchi K, Mashimo T

Neuroreport 2001 Jul 20;12(10):2079-2084

Pro-inflammatory cytokines have been shown to be involved in the genesis, persistence, and severity of neuropathic pain following nerve injury. The transcription factor, nuclear factor-kappa B (NF-kappaB), plays a pivotal role in regulating pro-inflammatory cytokine gene expression. To elucidate the role of NF-kappaB in the pathogenesis of neuropathic pain, using a gene-

based approach of NF-kappaB decoy, we tested whether the activated NF-kappaB affected pain behavior via the expression of inflammatory mediators. Single endoneurial injections of NF-kappaB decoy, at the site of nerve lesion, significantly alleviated thermal hyperalgesia for up to 2 weeks and suppressed the expression of mRNA of the inflammatory cytokines, iNOS, and adhesion molecules at the site of nerve injury. This finding suggests that a perineural inflammatory cascade, that involves NF-kappaB, is involved in the pathogenesis of neuropathic pain.

Etanercept reduces hyperalgesia in experimental painful neuropathy

Sommer C, Schafers M, Marziniak M, Toyka KV

J Peripher Nerv Syst 2001 Jun;6(2):67-72

Etanercept, a recombinant tumor necrosis factor receptor (p75)-Fc fusion protein competitively inhibits tumor necrosis factor-alpha (TNF). Etanercept has been successfully used in patients with rheumatoid arthritis, where it reduces pain and inflammation. Because locally produced proinflammatory cytokines play a role in pain after nerve injury, we investigated whether etanercept can reduce pain and hyperalgesia in an animal model of painful neuropathy, the chronic constriction injury of the sciatic nerve. C57BL/6 mice received etanercept or sham treatment by local near-nerve injection to the injured nerve or by systemic application. Treatment with etanercept reduced thermal hyperalgesia and mechanical allodynia significantly in both modes of application. The effect of etanercept was present in animals that were treated from the time of surgery and in those that were treated from day 6, when hyperalgesia was already present. These results suggest the potential of etanercept as a treatment option for patients with neuropathic pain.

Flecainide reverses neuropathic pain and suppresses ectopic nerve discharge in rats

Ichimata M, Kitano T, Ikebe H, Iwasaka H, Noguchi T

Neuroreport 2001 Jul 3;12(9):1869-73

We investigated effects of flecainide, a Class IC sodium channel blocker, in the rat chronic constrictive injury (CCI) and ectopic nerve discharge models. In the behavioral evaluation, 2, 6, and 12 mg/kg flecainide were intravenously given to the CCI model, and a dose-dependent analgesic effect was shown on both thermal hyperalgesia and tactile allodynia. In the electrophysiological evaluation using the ectopic nerve discharge model produced by saphenous neurectomy, i.v. administration of 2, 6, and 12 mg/kg flecainide suppressed spontaneous discharge at the peripheral nerve level in a dose-dependent fashion as with the behavioral evaluation, but flecainide did not affect nerve conduction at the dose of 12 mg/kg.

Effect of gabapentin and lamotrigine on mechanical allodynia-like behaviour in a rat model of trigeminal neuropathic pain

Christensen D, Gautron M, Guilbaud G, Kayser V

Pain 2001 Aug;93(2):147-53

Injury to the trigeminal nervous system may induce severe pain states. This study examined the antinociceptive effect of the novel anticonvulsants, gabapentin and lamotrigine, in a rat model of trigeminal neuropathic pain produced by chronic constriction of one infraorbital nerve. Responsiveness to von Frey filament stimulation of the vibrissal pad was evaluated 2 weeks post-operation. Hyper-responsive rats received acute and repeated (five injections separated by the half-life of the compound) injections with gabapentin and lamotrigine. 76% of the nerve-injured rats displayed pronounced hyper-responsiveness (median 0.217 g (lower-upper percentiles 0.217-0.217) vs. 12.5 g pre-operative), that was resistant to both single (5-100 mg/kg) and repeated (5-30 mg/kg) injections with i.p. lamotrigine. Repeated (30 and 50 mg/kg), but not single (30-100 mg/kg) injections of i.p. gabapentin partially alleviated the mechanical allodynia-like behaviour. Repeated injections of gabapentin at 50 but not at 30 mg/kg produced motor deficits. The results indicate that gabapentin rather than lamotrigine may be a better therapeutic approach for the clinical management of some trigeminal neuropathic pain disorders.

Mapping a gene for neuropathic pain-related behavior following peripheral neurectomy in the mouse

Seltzer Z, Wu T, Max MB, Diehl SR

Pain 2001 Aug;93(2):101-6

Total hindpaw denervation in rodents elicits an abnormal behavior of licking, scratching and self-injury of the anesthetic limb ('autotomy'). Since the same denervation produces phantom limb pain and anesthesia dolorosa in humans, autotomy has been used as a model of human neuropathic pain. Autotomy is an inherited trait in rodents, attributable to a few genes of major effect. Here we used recombinant inbred (RI) mouse lines of the AXB-BXA RI set to map a gene for autotomy. Autotomy levels following unilateral sciatic and saphenous nerve section were scored daily for 36 days, using a standardized scale, in all 23 RI lines available for this set. We used a genetic map of 395 marker loci and a permutation-based statistical method for categorical data to assess the statistical significance of mapping results. We identified a marker on chromosome 15 with statistical support ($P=0.0003$) in the range considered significant for genome-wide scans in the mouse. Several genes located in this chromosomal region encode for neural functions related to neuropathic pain and may indicate targets for development of novel analgesics.

A-134974: a novel adenosine kinase inhibitor, relieves tactile allodynia via spinal sites of action in peripheral nerve injured rats

Zhu CZ, Mikusa J, Chu KL, Cowart M, Kowaluk EA, Jarvis MF, McGaraughty S

Brain Res 2001 Jun 29;905(1-2):104-10

Extracellular levels of adenosine (ADO) can be raised through inhibition of adenosine kinase (AK), a primary metabolic enzyme for ADO. AK inhibitors have shown antinociceptive activity in a variety of animal models of nociception. The present study investigated the antinociceptive actions of a novel and selective AK inhibitor, A-134974 (IC(50)=60 pM), in a rat model of neuropathic pain (ligations of the L5/L6 spinal nerves) and explored the relative contributions of supraspinal, spinal and peripheral sites to the actions of A-134974. Systemic A-134974 dose-dependently reduced tactile allodynia (ED(50)=5 µg/mol/kg, i.p.) for up to 2 h. Fall latencies in the rotarod test of motor coordination were unaffected by systemic administration of A-134974 (at doses up to 30 µg/mol/kg, i.p.). Administration of A-134974 intrathecally (i.t.) was more potent (ED(50)=10 nmol) in relieving tactile allodynia than delivering the compound by intracerebroventricular (ED(50)>100 nmol, i.c.v.) or intraplantar (ED(50)>500 nmol) routes suggesting that spinal sites of action are the primary contributors to the anti-allodynic action of A-134974. The anti-allodynic effects of systemic A-134974 (10 µg/mol/kg, i.p.) were antagonized by the non-selective ADO receptor antagonist, theophylline (30-500 nmol) administered i.t. These data demonstrate that the novel AK inhibitor A-134974 potently reduces tactile allodynia through interactions with spinal sites and adds to the growing evidence that AK inhibitors may be useful as analgesic agents in a broad spectrum of pain states.