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Increased blood flow and erythema in the posterior vestibular mucosa in vulvar vestibulitis.

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

Obstet Gynecol 2001 Dec;98(6):1067-74

OBJECTIVE: To evaluate vascular changes as a possible underlying cause of mucosal erythema in women with vulvar vestibulitis. METHODS: Laser Doppler perfusion imaging was used to map the superficial blood flow in the vestibular mucosa in 20 women with vestibulitis and in 21 healthy control subjects. A possible correlation between perfusion values and graded erythema (1-5) around the vaginal introitus was analyzed. Changes in microvascular density in the posterior part of the mucosa were investigated in sections from ten patients and ten controls by a computer-assisted image-processing program. Induced vasoconstriction of terminal arterioles in the same posterior area was also studied. RESULTS: Significant increases in perfusion values were registered in the posterior parts of the vestibular mucosa in patients compared with controls. The highest blood flow was registered in the posterior fourchette. The most pronounced erythema was also located in the posterior vestibule in the patients. However, there was no significant correlation between perfusion values and degree of erythema in the same individual. The microvascular density or the ability of vestibular arterioles to constrict did not differ between patients and controls. CONCLUSION: Women with vestibulitis have an increased superficial blood flow and erythema in the posterior parts of the vestibular mucosa. The increased perfusion, most probably caused by a neurogenic vasodilatation contributes to, but does not fully explain the erythema. Atrophic changes of the surface epithelium should also be considered in the evaluation of an erythema.

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Vulvodynia-new and more effective approaches to therapy.

Bates CM, Timmins DJ

Int J STD AIDS 2002 Mar;13(3):210-2

Two cases are described of treatment-resistant vulvodynia that responded well to gabapentin. Gabapentin, an anti-epileptic drug, has been used in the treatment of neuropathic pain such as diabetic neuropathy and post-herpetic neuralgia. However, there has been little experience of its use in the relief of symptoms in vulvodynia and we add our observations to the one report of its use in these circumstances that has been published so far.

Psychological and sexual functioning in women with vulvar vestibulitis.

Gates EA, Galask RP

J Psychosom Obstet Gynaecol 2001 Dec;22(4):221-8

OBJECTIVE: The purpose of the study was to compare psychological and sexual functioning in women with vestibulitis with healthy controls. It was hypothesized that women with vestibulitis would experience greater psychological stress and sexual dissatisfaction than controls. STUDY DESIGN: Fifty-two women with vestibulitis recruited from a vulvovaginal disease clinic and 46 healthy controls recruited from an outpatient gynecology clinic completed five standardized measures of psychological and sexual functioning. Multivariate analyses of variance and covariance were used to examine group differences. RESULTS: Women with vestibulitis reported significantly higher scores than controls on the measures of depression ($p < or = 0.001$), psychological distress ($p < or = 0.001$) and sexual depression ($p < or = 0.001$). They reported significantly lower scores on the measures of sexual satisfaction ($p < or = 0.001$), sexual behavior ($p < or = 0.001$) and sexual self-esteem ($p < or = 0.01$). CONCLUSION: The results of this study highlight the importance of addressing psychological distress and sexual dissatisfaction in women with vestibulitis.

Nortriptyline for depression and vulvodynia.

Stolar AG, Stewart JT

Am J Psychiatry 2002 Feb 1;159(2):316-317

Vulvar vestibulitis syndrome: an overview of non-surgical treatment.

Mariani L

Eur J Obstet Gynecol Reprod Biol 2002 Mar 10;101(2):109-12

Vulvar vestibulitis syndrome, which represents one of the major cause

of dyspareunia, is a puzzling clinical entity. Although many treatment options have been employed, a rationale therapeutic strategy is still not stated. The present article reviews the most popular medical approaches of such entity (biofeedback, tricyclic antidepressants, interferon psychologic-behavioural therapy, diet modification), as well as those to avoid.Tricyclic antidepressants and biofeedback of the pelvic floor muscles represents the first line effective therapy. Moreover, psychological counselling must support any treatment options.

The male genital skin burning syndrome (Dysaesthetic Peno/Scroto-dynia).

Markos AR

Int J STD AIDS 2002 Apr;13(4):271-2

en may complain of penile and/or scrotal skin burning with no evidence of positive physical signs or investigations. The condition is cumbersome and leads to stress and disruption in social and sexual relationships. The patients report no response to previous medications (including antibiotics, antifungals and topical corticosteroids); and identify improvement in symptoms and quality of life on selective serotonin re-uptake inhibitors (SSRI). A similar condition has been recognized in the female patients (dysaesthetic vulvodynia). We report the occurrence of this condition in three men and suggest it being recognized as 'the male genital skin burning syndrome' (Dysaesthetic Peno/Scroto-dynia).

Influence of interleukin-1 receptor antagonist gene polymorphism on disease.

Witkin SS, Gerber S, Ledger WJ.

Clin Infect Dis 2002 Jan 15;34(2):204-209

Interleukin-1 receptor antagonist (IL-1RA) is a naturally occurring competitive inhibitor of interleukin-1 (IL-1)-induced proinflammatory activity. The IL-1RA gene is polymorphic, resulting in quantitative differences in both IL-1RA and IL-1beta production. Persons homozygous for allele 2 of the IL-1RA gene (IL1RN*2) have a more prolonged and more severe proinflammatory immune response than persons with other IL-1RA genotypes. Thus, being IL1RN*2 homozygous might be beneficial when combating infectious agents or malignantly transformed cells, but it might be detrimental for those with chronic inflammatory conditions or who are pregnant. The IL1RN*2 phenotype is associated with ulcerative colitis and Crohn's disease, lupus erythematosus, vulvar vestibulitis, and possibly with osteoporosis and coronary artery disease. IL1RN*2 homozygosity may also be associated with recurrent spontaneous abortion, preterm birth, and severity of preeclampsia. Conversely, there are negative associations between IL1RN*2 homozygosity and vaginal colonization with mycoplasmas, infection with human cytomegalovirus and Epstein-Barr virus, human immunodeficiency virus proliferation, and the occurrence of ovarian cancer.

Skin diseases affecting the vulva.

Salim A, Wojnarowska F

Current Obstetrics & Gynaecology, p 81-89, Vol 12, Number 2, April 2002

Skin diseases of the vulva are associated with considerable morbidity and often reluctance on the part of patients to seek medical attention. The most common conditions seen in a dermatology vulval clinic are the vulval dermatoses (inflammatory disorders), which comprise lichen sclerosus, lichen planus, vulval eczema and psoriasis. Other conditions such as vulval pain syndromes, vulval disorders associated with systemic diseases and blistering diseases are also seen. Treatment of many of these conditions involves the use of potent topical steroids, which are safe to use under supervision and in the short term.

Management of anogenital lichen sclerosus.

Neill SM, Ridley CM

Clin Exp Dermatol 2001 Nov;26(8):637-43

Lichen sclerosus (LS) is a skin condition that affects genital and extra genital epithelia in both males and females of all ages and it may occur in association with other autoimmune disease. Currently, the first line effective treatment is an ultra-potent topical corticosteroid. The long-term sequelae of LS include scarring, malignancy, which is rare, and psychosexual disfunction, which is common.

Perineoplasty for the treatment of introital stenosis related to vulvar lichen sclerosus.

Rouzier R, Haddad B, Deyrolle C, Pelisse M, Moyal-Barracco M, Paniel BJ.

Am J Obstet Gynecol 2002 Jan;186(1):49-52

OBJECTIVE: The objective of this study is to assess the usefulness of perineoplasty for introital stenosis related to vulvar lichen sclerosus. STUDY DESIGN: The records of 64 patients who underwent perineoplasty for this indication were reviewed retrospectively. The median age of patients was 49 years, and the median duration of lichen sclerosus was 60 months. Ninety percent of patients complained of dyspareunia. Patient satisfaction with the outcome was assessed by means of a questionnaire. Persistence of dyspareunia and impaired quality of sexual intercourse were considered as treatment failure. Risk factors of failure that were evaluated included duration of lichen sclerosus, age, previous topical steroid therapy, previous perineotomy, time since surgery, and histologic stage. Statistical analysis was

performed by use of Fisher exact test. RESULTS: Of the 64 patients, 12 were lost to follow-up and 2 patients did not respond to the questionnaire. Perineoplasty improved dyspareunia in 45 of the 50 patients (90%) and quality of sexual intercourse in 43 of 50 patients (86%). None of the risk factors evaluated were associated with failure of perineoplasty. CONCLUSION: Perineoplasty provides good functional results for women with introital stenosis related to vulvar lichen sclerosus.

Over-the-counter antifungal drug misuse associated with patient-diagnosed vulvovaginal candidiasis.

Ferris DG, Nyirjesy P, Sobel JD, Soper D, Pavletic A, Litaker MS

Obstet Gynecol 2002 Mar;99(3):419-25

OBJECTIVE: To estimate what proportion of symptomatic women purchasing over-the-counter antifungal products for immediate treatment of presumed vulvovaginal candidiasis have vulvovaginal candidiasis or other genitourinary conditions. METHODS: A time-location sample of 95 symptomatic women who purchased and presented with an over-the-counter antifungal product for immediate and personal treatment of presumed vulvovaginal candidiasis were evaluated by clinical examination and pertinent laboratory tests. The percentage of women diagnosed having vulvovaginal candidiasis or other conditions, proportions of women with vulvovaginal candidiasis compared between groups with and without a prior diagnosis of vulvovaginal candidiasis, and groups that read or did not read the over-the-counter package label were assessed. RESULTS: The actual diagnoses for women who self-diagnosed vulvovaginal candidiasis were: vulvovaginal candidiasis 33.7%, bacterial vaginosis 18.9%, mixed vaginitis 21.1%, normal 13.7%, other diagnoses 10.5%, and trichomonas vaginitis 2.1%. Women with a previous clinically based diagnosis of vulvovaginal candidiasis were not more accurate in diagnosing vulvovaginal candidiasis than women without a prior clinical diagnosis (chi(2) = 0.27, P =.6). Women who read the package label were no more likely to have vulvovaginal candidiasis than were women who did not read the label (Fisher exact test, P =.39). CONCLUSION: Many women who self-diagnose and use an over-the-counter product for treatment of presumed vulvovaginal candidiasis do not have vulvovaginal candidiasis. A history of a previous clinically based diagnosis of vulvovaginal candidiasis and reading the package label do not help women self-diagnose vulvovaginal candidiasis properly. Ready access to these products is associated with wasted financial expenditures, unfulfilled expectations, and a delay in correct diagnosis for a substantial number of women.

Vulval disease in pre-pubertal girls.

Fischer GO

Australasian Journal of Dermatology, Vol 42 Issue 4 Page 225 - Nov 2001

Children present with vulval complaints less frequently than do adults;

although there are many similarities between paediatric and adult groups of patients with vulval disease, there are also important differences. In both groups, dermatitis, psoriasis and lichen sclerosus are the most frequently seen dermatoses. Birthmarks and congenital abnormalities presenting for the first time are more of an issue in children than in adults. Fusion of the labia and streptococcal vulvovaginitis are conditions seen only in the paediatric group. Sexually transmitted diseases such as genital warts and genital herpes are not common in this group and should always raise the possibility of child sexual abuse. Chronic vulvovaginal candidiasis, although a very common problem in adult patients, is not seen in the prepubertal group.

New, simple, ultrasound-guided infiltration of the pudendal nerve.

Kovacs P, Gruber H, Piegger J and Bodner G

DISEASES OF THE COLON & RECTUM 2001;44:1381-1385

PURPOSE: Anesthetic infiltration of the pudendal nerve at the ischial spine can relieve perineal pain in cases of compression or distention. The aim of our study was to look for a real-time, visually controlled infiltration technique using ultrasound. METHODS: Fifty-three volunteers were examined in a prone position using a 3.5-MHz curved-array probe in color-coded Doppler mode. The deep gluteal region was scanned in two perpendicular planes, longitudinal and transverse to the internal pudendal artery. RESULTS: On the transverse planes the ischial spine, the sacrospinous ligament, and the internal pudendal artery were depicted in all but two cases. In 47.2 percent of the cases one trunk of the pudendal nerve was detected directly. Nerves consisting of more than one trunk were not found. The thickness of the nerve ranged between 3.5 and 7 mm. CONCLUSIONS: In almost one-half of the cases a direct ultrasound-guided infiltration of the pudendal nerve is possible. In the remaining cases the nerve can be detected and blocked indirectly, using the ischial spine or the internal pudendal artery as a landmark.

Sacral nerve stimulation in patients with chronic intractable pelvic pain.

Siegel S, Paszkiewicz E, Kirkpatrick C, Hinkel B and Oleson K

THE JOURNAL OF UROLOGY 2001;166:1742-1745

Purpose: Transforamenal sacral nerve stimulation with an implantable neuroprosthetic device has been shown to benefit patients with chronic voiding dysfunction. In this study we measured the effectiveness of sacral nerve stimulation in 10 patients with chronic intractable pelvic pain. Materials and Methods: After successful percutaneous trial stimulation, a neuroprosthetic sacral nerve stimulation device was surgically implanted in 10 patients with chronic intractable pelvic pain. Leads were placed in the S3 and S4 foramen in 8 and 2 cases, respectively. Patients were evaluated throughout the study using a patient pain assessment questionnaire on a scale of 0-absent to 5-

excruciating pain. Pain was assessed at baseline, during test stimulation, and 1, 3 and 6 months after surgical lead implantation. An additional long-term assessment was done at a median followup of 19 months. Results: Of the 10 patients with the implant 9 had a decrease in the severity of the worst pain compared to baseline at a median followup of 19 months. The number of hours of pain decreased from 13.1 to 6.9 at the same followup interval. There was also an average decrease in the rate of pain from 9.7 at baseline to 4.4 on a scale of 10-always to 0-never having pain. At a median of 19 months 6 of 10 patients reported significant improvement in pelvic pain symptomology. Conclusions: These data imply that transforamenal sacral nerve stimulation can have beneficial effects on the severity and frequency of chronic intractable pelvic pain. Future clinical studies are necessary to determine the long-term effectiveness of this therapy.

Gabapentin in the treatment of chronic intractable pain.

Gustorff B, Nahlik G, Spacek A, Kress HG

Schmerz 2002 Feb;16(1):9-14

INTRODUCTION: Gabapentin has been shown to reduce pain associated with diabetic neuropathia and postherpetic neuralgia. To date it is not known, whether gabapentin is generally effective in other types of pain. It was therefore the aim to study gabapentin in patients suffering from intractable pain with respect to efficacy, predictive factors and side effects. METHODS: Retrospective analysis of the data sheet of pretreated patients suffering from intractable pain and treated with gabapentin as a third line drug at a university pain clinic. Pain intensity (visual analogue scale, VAS 0--10 cm), pain characteristics, diagnosis, pre- and co-treatment, and side effects were assessed. Response to treatment was defined as a 50% reduction in pain or a pain intensity of VAS [less-than-or-equal]3. RESULTS: 99 patients were included. Approximately half the patients (n = 49) responded to gabapentin. Patients suffering from neuropathic pain showed a higher response rate (60%) compared to patients with muscle-sceletal pain (35%). Allodynia was twice as high in the responders (35%) compared to the non-responders (18%) before treatment. No serious side effects were reported. CONCLUSION: Gabapentin was effective in approximately 50% of pretreated patients with intractable pain. Neuropathic pain responded better than pain of other origine. Allodynia may be a predictive factor for a positive treatment effect.

Open label trial of oxcarbazepine in neuropathic pain.

Royal M, Wienecke G, Movva V, Ward S, Bhakta B, Jensen M and Gunyea I

Pain Medicine 2 (3), 250-251

We evaluated the use of a new anticonvulsant, oxcarbazepine (Trileptal®, Novartis Pharmaceuticals), in 24 consecutive patients (19 females, 3 males) with neuropathic pain who were nonresponders to gabapentin (Neurontin®, Parke Davis). Oxcarbazepine was FDA-approved in early 2000 for add-on treatment of partial seizures in adults. It is

a keto-analog of carbamazepine that is rapidly converted to a monohydroxy derivative that is the active drug. It is a membrane stabilizer and a weak hepatic induce without autoinduction. It has demonstrated comparable efficacy to carbamazepine in trigeminal neuralgia with fewer side effects. Unlike carbamazepine, oxcarbazepine has no bone marrow suppression or hepatotoxicity. All patients were started on 300 mg daily and were asked to increase to 300 mg twice daily at 1 week and then further increases were made at weekly intervals as tolerated. Responses were characterized as follows: excellent (greater than 70% reduction in neuropathic symptoms), good (50-70% improvement), fair (20-50% improvement) and poor (less than 20% improvement). The following results were obtained: excellent = 12.5%, good = 20.8%, fair = 20.8%, and poor = 45.8%. Only 6 patients had mild to moderate adverse events (nausea, vomiting or dizziness in 4 patients, skin rash in 1 patient and edema in 1 patient). At the time of this report, all but 2 of the patients had not increased beyond 600 mg q.d. indicating the potential for even better response rates at higher doses, as was seen in two of the excellent responders who did not achieve their effect until 900-1200 mg. Oxcarbazepine is a well-tolerated option for treating refractory neuropathic pain.

Double-blind, randomized trial of bupropion SR for the treatment of neuropathic pain.

Semenchuk MR, Sherman S, Davis B

Neurology 2001;57:1583-1588

Objective: To evaluate the effectiveness and safety of bupropion sustained-release (SR) for the treatment of neuropathic pain. Method: This single-center, outpatient, randomized, double-blind, placebo-controlled, crossover study consisted of two phases. Forty-one nondepressed patients with neuropathic pain spent 6 weeks in each phase in random order and received identical tablets of 150 mg bupropion SR or placebo. Patients were instructed to take one tablet once daily for 1 week followed by one tablet twice daily for 5 weeks. Results: While the patients took bupropion SR, neuropathic pain relief was improved or much improved in 30 (73%) patients, and one of these patients became pain-free. The mean average pain score at baseline was 5.7, which remained unchanged at the end of week 6 with placebo, but decreased by 1.7 points to 4.0 ($p < 0.001$) during therapy with bupropion SR. Pain relief with bupropion SR was significant at week 2 ($p < 0.05$) and continued throughout weeks 3 through 6 ($p < 0.001$). A significant decrease in interference of pain on quality of life was observed while patients were receiving bupropion SR compared with placebo. Side effects experienced with bupropion SR were not dose-limiting and consisted primarily of dry mouth, insomnia, headache, gastrointestinal upset, tremor, constipation, and dizziness. Conclusion: This placebo-controlled crossover trial showed that bupropion SR (150-300 mg daily) was effective and well tolerated for the treatment of neuropathic pain.

Use of transmucosal fentanyl in non-malignant, chronic pain.

Tennant F and Hermann L

Pain Medicine 2 (3), 252-253

Transmucosal fentanyl (TF) has recently become available for treatment of breakthrough pain in cancer patients who are already tolerant to opioids. In addition to cancer patients, there is a growing number of chronic pain patients who regularly use and are tolerant to opioids and require a breakthrough opioid for adequate pain control. This pilot study was done to determine if TF is effective and acceptable to non-malignant, chronic pain patients who are opioid tolerant and require a breakthrough opioid(s) for pain control. Sixty patients with chronic, non-malignant pain who were maintained on a long-acting opioid and who required breakthrough pain control were given TF in an initial dose of 400 or 600 mcg per single, transmuscosal administration. Among the study group 35 (58.3%) experienced chronic pain due to injuries to the spine and 25 (41.7%) were due to medical conditions other than cancer. After at least three months of usage, patients were asked if they desired to continue TF and the reason(s) why they believed it to be effective. Fifty-eight (96.7%) of these subjects perceived that TF was an effective breakthrough opioid and desired to continue it. The single, effective dosage ranged from 800 to 1600 mcg per administration, and the number of separate monthly dosages ranged from 2 to 360. The majority of patients used TF only for emergency, pain purposes but others preferred TF as their major breakthrough opioid and ceased use of other short-acting opioids including injectable meperidine. Reported reasons for widespread patient acceptance included TF's fast action, fewer bed-bound days, increased energy, decreased use of other opioids, less depression, and fewer emergency room visits. This pilot study indicates that TF is effective and desired as a preferential opioid for breakthrough pain by a high percentage of chronic, non-malignant pain patients.

Nerve blocks in chronic pain therapy - are there any indications left?

Stanton-Hicks M

Acta Anaesthesiol Scand 2001 Oct;45(9):1100-7

Although diagnostic imaging is now highly developed, neural blockade provides another opportunity to test for a source of pain that may frequently leave no signature. Likewise, many neuropathic pains can not be tested by neurodiagnostic methods. This paper makes a case for the continued use of regional anesthesia to assist in the diagnosis and therapy of chronic pain. In particular, the example of autonomic blocks and blocks of the axial spine are emphasized. Nerve blocks require an understanding of the anatomy, physiology, pharmacology, and the ability to interpret critically their results.

Nociception, pain, and antinociception: current concepts.

Riedel W, Neeck G

Z Rheumatol 2001 Dec;60(6):404-15

The physiology of nociception involves a complex interaction of peripheral and central nervous system (CNS) structures, extending from the skin, the viscera and the musculoskeletal tissues to the cerebral cortex. The pathophysiology of chronic pain shows alterations of normal physiological pathways, giving rise to hyperalgesia or allodynia. After integration in the spinal cord, nociceptive information is transferred to thalamic structures before it reaches the somatosensory cortex. Each of these levels of the CNS contain modulatory mechanisms. The two most important systems in modulating nociception and antinociception, the N-methyl-D-aspartate (NMDA) and opioid receptor system, show a close distribution pattern in nearly all CNS regions, and activation of NMDA receptors has been found to contribute to the hyperalgesia associated with nerve injury or inflammation. Apart from substance P (SP), the major facilitatory effect in nociception is exerted by glutamate as the natural activator of NMDA receptors. Stimulation of ionotropic NMDA receptors causes intraneuronal elevation of Ca2+ which stimulates nitric oxide synthase (NOS) and the production of nitric oxide (NO). NO as a gaseous molecule diffuses out from the neuron and by action on guanylyl cyclase, NO stimulates in neighboring neurons the formation of cGMP. Depending on the expression of cGMP-controlled ion channels in target neurons, NO may act excitatory or inhibitory. NO has been implicated in the development of hyperexcitability, resulting in hyperalgesia or allodynia, by increasing nociceptive transmitters at their central terminals. Among the three subtypes of opioid receptors, mu- and delta-receptors either inhibit or potentiate NMDA receptor-mediated events, while kappa opioids antagonize NMDA receptor-mediated activity. Recently, CRH has been found to act at all levels of the neuraxis to produce analgesia. Modulation of nociception occurs at all levels of the neuraxis, thus, eliciting the multidimensional experience of pain involving sensory-discriminative, affective-motivational, cognitive and locomotor components.

Novel local anaesthetics and novel indications for local anaesthetics.

Hollmanna MW, Durieuxa ME and Graf BM

CURRENT OPINION IN ANAESTHESIOLOGY 2001;14:741-749

Research into local anaesthetic mechanisms over the past few years has focused on two main issues. First, attention has focused on development of compounds with fewer side effects, better sensory/motor separation and longer duration of action; this has resulted in the introduction of ropivacaine and levobupivacaine into clinical practice. These agents have a lesser cardiotoxic effect than older compounds, and ropivacaine may in addition offer better sensory/motor separation. Several other compounds, including tonicaine and sameridine, are under investigation. In addition, the local anaesthetic properties of amitryptiline are being studied, and liposome encapsulation of local anaesthetics appears able to confer new pharmacokinetic properties on common drugs. Second, the molecular basis for several local anaesthetic actions that are not mediated by sodium channels has become a topic of interest. The mechanisms that underlie anti-inflammatory and antithrombotic actions are at present being unravelled. How local anaesthetics potentiate

antitumour agents, protect neuronal tissue and prevent bronchial reactivity is less clear, but the potential clinical benefits of these effects deserve further exploration.

Chronic neuropathic pain: Pathomechanism and pharmacology

Urban L, Nagy I, Bevan SJ

Drug Development Research, Volume 54, Issue 3, 2001. Pages: 159-166

Neuropathic pain syndromes form a group of loosely connected diseases linked by the common presence of injury/damage to the peripheral sensory system and the resulting effect: chronic pain. Treatment of patients suffering from neuropathic pain is one of the most challenging clinical tasks as classical painkillers such as opioids and nonsteroidal anti-inflammatory drugs lack antinociceptive effect in these syndromes. The recent development of various animal models aided our understanding of neuropathic pain and provided targets for analgesic intervention. The discovery of abnormal, ectopic activity in injured primary afferents, sprouting of large calibre primary afferent fibres to the superficial dorsal horn, and changes in protein expression in DRG (dorsal root ganglion) cells after injury has highlighted differences between the pathomechanisms of nociceptive and neuropathic pain and explained the lack of efficacy of commonly used analgesic drugs. Recent clinical trials based on considerations from animal studies have proved, at least partly, that targeting these mechanisms could lead to more efficacious antinociceptive agents for neuropathic pain syndromes. There are three major sites of interventions: (1) abnormal, ectopic activity of the injured afferents, (2) increased release of transmitters in the spinal cord, and (3) enhanced neuronal activity in the spinal dorsal horn. To date, there has been no breakthrough in the clinical treatment of neuropathic pain; however, data from recent preclinical studies and clinical trials with anticonvulsants, gabapentin-like molecules, Ca (calcium)-channel blocking agents, GABAB (-amino butyric acid) receptor agonists, and NMDA (N-methyl-D-asparate) receptor antagonists promise the development of effective pain relief for patients suffering from neuropathic pain.

Anti-epileptic drugs for pain management.

Burton AW

The Internet Journal of Pain, Symptom Control and Palliative Care (2001)

http://www.ispub.com/journals/IJPSP/Vol1N2/pain-a.html

Antiepileptic drugs (AED's) depress abnormal neuronal discharges and raise the threshold for neural impulse propagation. They have been found to have therapeutic efficacy in neuropathic pain states. Carbamazepine(CZ) and phenytoin (PT) were the drugs of choice for treating trigeminal neuralgia for 40 plus years. These two agents have been largely replaced due to the introduction of many newer, better-

tolerated, and safer antiepileptic drugs.

Alpha2 receptors and agonists in pain management.

Smith H and Elliott J

CURRENT OPINION IN ANAESTHESIOLOGY 2001;14:513-518

Alpha2 agonists have been in clinical use for decades, primarily in the treatment of hypertension. In recent years, alpha2 agonists have found wider application, particularly in the fields of anesthesia and pain management. It has been noted that these agents can enhance analgesia provided by traditional analgesics, such as opiates, and may result in opiate-sparing effects. This has important implications for the management of acute postoperative pain and chronic pain states, including disorders involving spasticity or myofascial pain, neuropathic pain, and chronic daily headaches. The clinical utility of these agents is ever expanding, as they are gaining broader use in neuraxial analgesia, and new applications are continuously under investigation. The alpha2 agonists that are currently employed in anesthesia and pain management include clonidine, tizanidine, and dexmedetomidine. Moxonidine and radolmidine, which are not currently in clinical use in humans, may offer favorable side-effect profiles when compared with traditional alpha2 agonists, and may thereby allow for more widespread pain management applications.

Pharmacology of peripheral analgesia.

Ness TJ

Pain Practice 1 (3), 243-254

Pain may begin in the periphery with activation of nociceptor transducers. The present article reviews the pharmacology of drug action at the level of the primary afferent by discussing the following: [1] agents which block transduction processes (vanilloids, sodium ion channel blockers, antiserotonergic agents, antipurinergic agents); [2] agents inhibiting the transducer site (opioids, cannabinoids, alpha adrenergic agents); [3] agents blocking transducer-based modulation processes (anti-inflammatories, antikinin agents, antitachykinins); and [4] agents which block primary afferent-related modification processes (antineurotrophins). There is a clear role for many of these agents in the treatment of inflammatory pain and they have potential benefits for neuropathic pain with peripheral triggers.

Pharmacology of opioid and nonopioid analgesics in chronic pain states.

Martin TJ and Eisenach JC

Vol. 299, Issue 3, 811-817, December 2001

Chronic pain represents a mixture of pathophysiologic mechanisms, a

complex assortment of spontaneous and elicited pain states, and a somewhat unpredictable response to analgesics. Opioids remain the mainstay of treatment of moderate to severe chronic pain, although there is little systematic examination to guide drug selection. Cyclooxygenase inhibitors play primarily an adjunctive role in chronic pain treatment. Agents with little activity in the treatment of acute pain, such as antidepressants, antiepileptics, and i.v. administered local anesthetics, are initiated in many patients and have significant long-term efficacy in some patients with chronic pain. The N-methyl-D-aspartate antagonist ketamine and the 2-adrenergic agonist clonidine exhibit activity in patients with acute or chronic pain and reduce opioid consumption, but are often poorly tolerated due to side effects. Topical treatment with capsaicin or lidocaine exhibits efficacy in a subset of patients, and invasive intrathecal treatment with opioids as well as clonidine, neostigmine, and adenosine may have advantages in some patients. Several laboratory models have been developed to mimic chronic pain states found in humans. Nerve injury has been induced in rats by a variety of means, resulting in mechanical allodynia and thermal hyperalgesia. A number of arthritic states have also been produced by means of chronic joint inflammation in rats. The pharmacology of these neuropathic and arthritic pain models generally resembles that found in the respective human conditions. Additional models of chronic pain, particularly visceral pain, have been developed; however, the pharmacology of these models is not well established at this time.

The proteinase-activated receptor 2 is involved in nociception.

Hoogerwerf WA, Zou L, Shenoy M, Sun D, Micci MA, Lee-Hellmich H, Xiao SY, Winston JH, Pasricha PJ

J Neurosci 2001 Nov 15;21(22):9036-42

The proteinase-activated receptor 2 is expressed on a subset of primary afferent neurons and may participate in the neurogenic component of inflammation. We hypothesized that this receptor may also play a role in neuronal sensitization and contribute to the pathogenesis of pain in inflammatory conditions such as pancreatitis. Using a specific proteinase-activated receptor 2 activating peptide, we found evidence of such sensitization in vitro in the form of enhanced capsaicin- and KCl-evoked release of calcitonin gene-related peptide, a marker for nociceptive signaling. We then demonstrated that injection of the proteinase-activated receptor 2 activating peptide into the pancreatic duct can activate and sensitize pancreas-specific afferent neurons in vivo, as measured by Fos expression in the dorsal horn of the spinal cord. These observations suggest that proteinase-activated receptor 2 contributes to nociceptive signaling and may provide a novel link between inflammation and pain.

P2X receptors and nociception.

Chizh BA and Illes P

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The potential importance for nociception of P2X receptors, the ionotropic receptors activated by ATP, is underscored by the variety of pain states in which this endogenous ligand can be released. Several important findings have been made recently indicating that P2X receptors can be involved in pain mechanisms both centrally and in the periphery. The roles of ATP at these two sites and the P2X receptor subtypes involved appear to be different. In the periphery, ATP can be released as a result of tissue injury, visceral distension, or sympathetic activation and can excite nociceptive primary afferents by acting at homomeric P2X3 or heteromeric P2X2/3 receptors. Centrally, ATP released from central afferent terminals or second order neurons can modulate neurotransmitter release or postsynaptically activate neurons involved in central nociceptive transmission, with P2X2, P2X4, P2X6, and some other receptors being potentially involved. Evidence from in vivo studies suggests that peripheral ATPergic mechanisms are most important under conditions of acute tissue injury and inflammation whereas the relevance of central mechanisms appears to be more limited. Furthermore, the release of ATP and P2X receptor-mediated afferent activation appear to have been implicated in visceral and neuropathic pain; the importance of the ATPergic component in these states needs to be investigated further. Thus, peripheral P2X receptors, and homomeric P2X3 and/or heteromeric P2X2/3 receptors in particular, constitute attractive targets for analgesic drugs. The development of selective antagonists of these receptors, suitable for a systemic in vivo use although apparently difficult, may prove a useful strategy to generate analgesics with a novel mechanism of action.

Estrogen replacement reverses ovariectomy-induced vaginal hyperalgesia in the rat.

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Objectives: The loss of ovarian function in women through aging or oophorectomy is often associated with the development of vaginal hyperalgesia that can be alleviated with estrogen replacement. This study examined if ovariectomy in rats would similarly give rise to vaginal hyperalgesia, and, if so, whether estrogen replacement would alleviate it. Methods: Female rats were trained to perform an operant response to escape vaginal distention delivered by inflating a balloon located in mid-vaginal canal. Percent escape responses to eight different volumes of distention measured in normally cycling rats were compared with measures made in the same rats following ovariectomy (OVX) or sham ovariectomy (shamOVX), and then, in the OVX group, estrogen replacement (OVX+E2). Pressures exerted by the eight volumes on the vaginal wall were also measured, thereby permitting assessment of vaginal tone. Results: Whereas overall escape response percentages after OVX, but not shamOVX, were significantly higher to the largest six distention volumes compared with responses during cycling, there were individual differences in the amount of hyperalgesia. Following OVX+E2, escape response percentages decreased in all but one rat. Vaginal tone after OVX, shamOVX or OVX+E2 did not differ from overall vaginal tone in cycling rats. Conclusions: Ovariectomy in rats evokes a

variable amount of vaginal hyperalgesia that can be alleviated by estrogen replacement in most cases. Thus, the ovariectomized rat appears to provide a useful model for the study of mechanisms underlying the dyspareunia that is associated with loss of ovarian function in women.

Animal models of nociception.

Le Bars D, Gozariu M and Cadden SW

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The study of pain in awake animals raises ethical, philosophical, and technical problems. We review the ethical standards for studying pain in animals and emphasize that there are scientific as well as moral reasons for keeping to them. Philosophically, there is the problem that pain cannot be monitored directly in animals but can only be estimated by examining their responses to nociceptive stimuli; however, such responses do not necessarily mean that there is a concomitant sensation. The types of nociceptive stimuli (electrical, thermal, mechanical, or chemical) that have been used in different pain models are reviewed with the conclusion that none is ideal, although chemical stimuli probably most closely mimic acute clinical pain. The monitored reactions are almost always motor responses ranging from spinal reflexes to complex behaviors. Most have the weakness that they may be associated with, or modulated by, other physiological functions. The main tests are critically reviewed in terms of their sensitivity, specificity, and predictiveness. Weaknesses are highlighted, including 1) that in most tests responses are monitored around a nociceptive threshold, whereas clinical pain is almost always more severe; 2) differences in the fashion whereby responses are evoked from healthy and inflamed tissues; and 3) problems in assessing threshold responses to stimuli, which continue to increase in intensity. It is concluded that although the neural basis of the most used tests is poorly understood, their use will be more profitable if pain is considered within, rather than apart from, the body's homeostatic mechanisms.