PAIN

Pain Supplement 6 (1999) S141–S147

Implications of recent advances in the understanding of pain pathophysiology for the assessment of pain in patients

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Abstract

As we approach the new millennium, it is clear that we are on the brink of a major change in clinical pain management. We are poised to move from a treatment paradigm that has been almost entirely empirical to one that will be derived from an understanding of the actual mechanisms involved in the pathogenesis of pain. When this is achieved, pain treatment will at last be rationally based. The implications of this are immense and will necessitate major changes in the way we classify pain, which until now has been based on disease, duration and anatomy, to a mechanism-based classification. In addition, the assessment, diagnosis and treatment of pain will change. The aim in the future will be to identify in individual patients what mechanisms are responsible for their pain and to target treatment specifically at those mechanisms. We present for discussion, a new approach for classifying pain, based on an analysis of mechanisms, and show how this could be used to assess pain clinically. Such kinds of pain assessment, which need to be designed to reveal as much as possible about mechanisms, are necessary for more sophisticated epidemiology and clinical research as well as for providing the outcome measures necessary for the evaluation of the efficacy of new treatments targeted at particular pain mechanisms. © 1999 International Association for the Study of Pain. Published by Elsevier Science B.V.

Keywords: Pain pathophysiology; Assessment of pain; Pathogenesis of pain

1. Introduction

The pain field is in the midst of a revolution driven by the application of modern molecular, cellular and systems neurobiological techniques. The success of this surge in basic science work is such that we have easily achieved more in the last decade in terms of understanding how pain is generated than in the last hundred years. It is clear, moreover, that this is only the beginning, the human genome project, the application of high throughput screening and combinatorial chemistry techniques together with the development of high resolution functional imaging techniques is going to accelerate progress in an exponential fashion.

When one considers that contemporary clinical pain management is still empirically derived, based largely on observations made by folk medicine and serendipity, it is clear that pain management has a lot of catching up to do, progress here has been much slower. The gulf between the DNA sequences of receptors and ion channels identified as being uniquely involved in producing pain, and the patient arriving at a clinic complaining of pain are immense. The challenge now is to bridge this gulf. In order to achieve this, however, we are going to have to have to radically change the way we approach the classification, assessment, diagnosis and treatment of pain. This is not going to be easy and many mistakes will be made but there is no turning back, the genie is out of the bottle.

We would like to propose a new way of analyzing pain based on the current understanding of pain mechanisms and show the implications of this for assessing pain in individual patients and for evaluating new forms of diagnosis and therapy. This analysis is dedicated to Pat Wall, the indisputable leader in the study of pain this century and whose quest for understanding pain at a conceptual level and its application to clinical pain problems has been an inspiration and a driving force in the field. Pat, although indisputably a great scientist and insightful clinician, has always also been an iconoclast, and we can think of no more fitting tribute than to propose, in his honor, the dismantling of the current clinical approach to pain which belongs, we argue, more to the 19th than the 21st century. The real challenge will be to replace current clinical practice with an approach based on the conceptual insights and tools the advances in basic science are beginning to present us. Here we propose some preliminary suggestions.

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0304-3959/99/$20.00
PII: S0304-3959(99)00148-7

1.1. Advances in the understanding of pain mechanisms

While the power of contemporary preclinical basic science is readily recognized in its success in elucidating the molecular mechanism of the action of current analgesics; the opiates (Keiffer et al., 1992; Matthes et al., 1996), NSAIDS (Mitchell et al., 1993) and sodium channel blockers (Akopian et al., 1996), as well as in identifying novel targets for potential analgesics such as the DRG specific VR1 (Tominaga et al., 1998), P2x3 (Chen et al., 1995), DRASIC (Waldmann et al., 1997) and SNS/SNS2 (Tate et al., 1998) receptors and ion channels, another major breakthrough has been achieved in recent years. This has been in the elucidation of pain mechanisms at a system level through the development of pain models in laboratory animals that mimic key aspects of human pain conditions (Bennett and Xie, 1988; Stein et al., 1988; Kim and Chung, 1992).

What has become clear from preclinical as well clinical studies is that multiple mechanisms operating at different sites and with different temporal profiles produce the sensation we call pain. Pain is not a homogeneous sensation, but a constellation of different sensitivities in normal and diseased states. The same symptom may be produced by different mechanisms and a single mechanism may elicit different symptoms. It is essential, moreover, to differentiate etiological factors or diseases/causative factors from pain mechanisms. Etiological factors are important in initiating pain mechanisms but it is the pain mechanisms that produce the pain symptoms. Since the same disease may activate different mechanisms, a disease-based classification is of use only for disease-modifying therapy, not for treating the pain. The same is true for a symptom-based classification. Symptoms are not equivalent to mechanisms, although they reflect them. We need both to try establishing the mechanisms that produce pain and develop tools to identify in individual patients what mechanisms are present (Woolf et al., 1998).

Pain elicited in normal individuals is the consequence of the activation of a subset of highly specialized primary sensory neurons, the high threshold nociceptors. The terminals of these sensory neurons are adapted so as to be activated only by intense or potentially damaging peripheral stimuli and are functionally quite distinct from low threshold sensory fibers which normally only generate innocuous sensations in response to non-damaging low intensity stimuli (Willis and Coggeshall, 1991). Nociceptor transduction mechanisms involve activation of temperature-sensitive receptor ion channels like the vanilloid receptors VR1 and VRL1, channels sensitive to intense mechanical deformation or stretch of the membrane, or chemosensitive receptors activated by purines, protons, amines, peptides, growth factors, and cytokines released from damaged tissue or inflammatory cells. The sensitivity of the peripheral terminal is not fixed, however, and either repeated peripheral stimulation, or changes in the chemical milieu of the terminal, particularly during inflammation, leads to alterations in the threshold for activation of the terminal, the phenomenon of peripheral sensitization (Reeh, 1994). Peripheral sensitization is likely to reflect changes in the channel kinetics both of the transduction ion channels (which detect the stimulus) and those ion channels in the terminal which determine membrane excitability and initiate conduct action potentials. Most of these alterations in excitability are the result of post-translational changes, such as phosphorylation of the terminal membrane bound proteins (Gold et al., 1996).

In addition to changes in the sensitivity of the nociceptor peripheral terminal, post-injury pain hypersensitivity is also an expression of changes in the excitability of neurons in the spinal cord central sensitization (Woolf, 1983). Input from nociceptors to the spinal cord both evoke an immediate sensation of pain that lasts for the duration of the noxious stimulus and also induce an activity-dependent functional plasticity in the dorsal horn that outlasts the stimulus. This is due to an increase in neuronal membrane excitability. The increased excitability is triggered by release from C-fiber terminals of excitatory amino acid and neuropeptide transmitters which act on postsynaptic iono- and metabotropic receptors to produce inward currents as well as activation of signal transduction cascades in the neuron. These result in activation of both serine/threonine as well as tyrosine kinases, which by phosphorylating membrane proteins, particularly the NMDA receptor, increase membrane excitability by changing ion channel properties. This boost in excitability recruits existing suprathreshold inputs to the dorsal horn neurons, such that inputs that previously did not elicit an output from the cell now begin to do so. In this way, the responses to noxious stimuli become exaggerated and inputs from low threshold sensory fibers begin to activate central pain transmission pathways. Central sensitization is a major contributor to inflammatory and neuropathic pain producing an NMDA-dependent brush or pinprick-evoked secondary hyperalgesia and a tactile allodynia (Koltzenburg et al., 1992a,b, 1994; Eide et al., 1994; Stubhaug et al., 1997). In inflammation this activity-dependent central plasticity is driven by input from sensitized afferents innervating the inflamed tissue. After nerve injury central sensitization is driven by ectopic activity in the injured fibers resulting from changes in the expression or distribution of ion channels (Devor et al., 1993; Novakovic et al., 1998). These central functional changes are contributed to by changes in the phenotype of sensory neurons. For example, substance P, which is normally expressed only in those sensory neurons with unmyelinated axons, begins to be expressed in a subpopulation of sensory neurons with myelinated axons after both inflammation and nerve injury (Noguchi et al., 1995; Neumann et al., 1996). This means that although central sensitization is normally only evoked by input in nociceptors, after nerve injury/inflammation, input from A fibers can begin to produce this phenomenon. One example of this is the development of a progressive

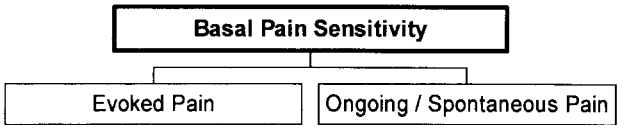

Fig. 1. Basal pain sensitivity is a term, which represents for an individual, the current status of their pain sensitivity and includes the pain they experience either spontaneously (i.e. in the absence of any identifiable stimulus) or that can be evoked directly by and within a short period of a defined stimulus.

tactile pain hypersensitivity with repeated touch of inflamed skin (Ma and Woolf, 1996, 1998).

In addition to an increase in membrane excitability triggered by peripheral nociceptor input, a decrease in phasic and tonic inhibition can also produce changes in dorsal horn excitability. This may result from a down-regulation of inhibitory transmitters or their receptors, a disruption of descending inhibitory pathways or a loss of segmental inhibitory interneurons in the dorsal horn (Woolf and Wall, 1982; Sugimoto et al., 1990; Castro-Lopes et al., 1993; Ren and Dubner, 1996).

After nerve injury, in addition to the development of ectopic excitability in the injured neurons, the establishment of central sensitization, phenotypic switches and disinhibition, a structural reorganization of central connections also occurs. This involves the sprouting or growth of the central terminals of low threshold mechanoreceptors from their normal termination site in the deep dorsal horn into lamina II, the site of termination of nociceptor C-fiber terminals (Woolf et al., 1992; Shortland and Woolf, 1993; Koerber et al., 1994; Koerber et al., 1995; Woolf et al., 1995). The sprouted low threshold A fibers make synaptic contact in lamina II with neurons that normally receive nociceptor input and this new pattern of synaptic input provides an anatomical substrate for tactile pain hypersensitivity.

1.2. Towards a new conceptual approach for understanding pain

Given the ongoing elucidation of some of the multiple mechanisms that operate to produce pain in normal and pathological conditions, it is appropriate to begin to evaluate how such mechanisms may fit into an overall schema related to pain production. We believe that key to this is the notion of basal pain sensitivity, a term which represents for an individual the current status of their pain sensitivity. Basal pain sensitivity represents the pain experienced either spontaneously (i.e. in the absence of any identifiable stimulus) or is evoked directly by and within a short period of a defined stimulus (Fig. 1). The basal sensitivity changes in response to the activation of different pain generating mechanisms.

In normal situations there is no spontaneous or background pain and pain is elicited only by intense or noxious mechanical, thermal or chemical stimuli, in a way such that the amplitude of the pain, beyond a clear threshold level, is determined by the intensity of the stimulus, and the localization and timing of the sensation reflects the site and duration of the stimulus. This constitutes a state of pain normosensitivity (Fig. 2). This is distinct from those conditions where there is an exaggerated pain sensitivity, or pain hypersensitivity, where pain may arise spontaneously, apparently in the absence of any peripheral stimulus, the response to noxious stimuli is exaggerated (hyperalgesia), may persist, radiate or become excessively amplified (hyperpathia) and normally innocuous stimuli may begin to produce pain (allodynia). Normosensitivity is also distinct from those situations where pain sensitivity is reduced, pain hyposensitivity, where suprathreshold noxious stimuli fail to elicit any pain response (Fig. 2).

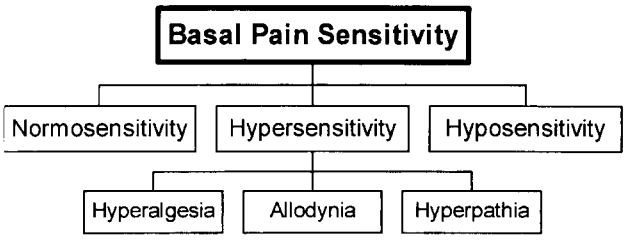

Fig. 2. Basal pain sensitivity can change in response to the activation of different pain promoting or suppressing mechanisms. In normal situations there is no spontaneous or background pain and pain is elicited only by intense or noxious mechanical, thermal or chemical stimuli. This constitutes pain normosensitivity. If pain arises spontaneously, or the response to noxious stimuli is exaggerated (hyperalgesia), persists, radiates or becomes excessively amplified (hyperpathia), or normally innocuous stimuli begin to produce pain (allodynia) this constitutes a state of pain hypersensitivity. If pain sensitivity is reduced such that suprathreshold noxious stimuli fail to elicit any pain response, this represents a state of pain hyposensitivity.

Pain hypersensitivity, defined in terms of spontaneous pain and an exaggerated response to stimuli (Fig. 1) may be produced in two distinct ways, by a stimulus-independent or stimulus-generated alteration of basal pain sensitivity (Fig. 3). Pain hypersensitivity that is generated or produced in a stimulus-independent way is a reflection of a change in the system that is not contingent on any prior or ongoing action potential traffic in the system, i.e. the non-activated or undisturbed system becomes pain hypersensitive where it will now respond to stimuli in an abnormal way. Fig. 4 illustrates some of the conditions that operate to produce stimulus-independent pain hypersensitivity. These include

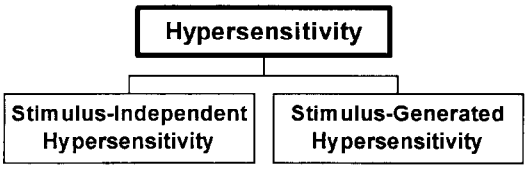

Fig. 3. Pain hypersensitivity, where basal pain sensitivity manifests as spontaneous pain or exaggerated responses to peripheral stimuli, can be produced in two distinct ways: either by a stimulus-independent series of mechanisms which are not contingent on any prior or ongoing action potential traffic in the system and a stimulus-generated series of mechanisms where the pain hypersensitivity is the direct consequence of activity which is responsible for the development of the hypersensitivity.

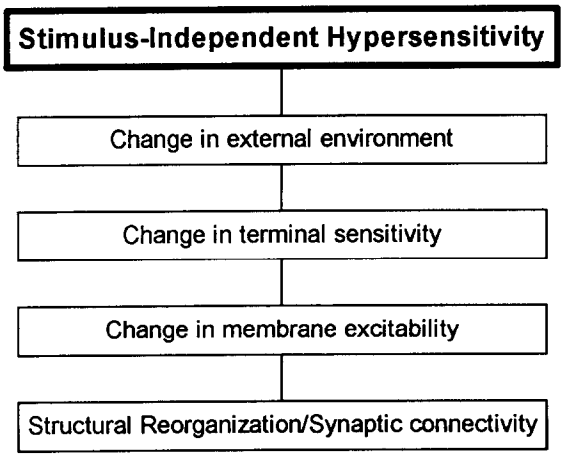

Fig. 4. Stimulus-independent pain hypersensitivity may result from a number of non-activity-dependent changes in the somatosensory system including changes in the chemical environment extrinsic to the terminal (e.g. presence of chemical activators for nociceptors), changes within the terminal (e.g. post-translational changes leading to a reduced threshold), alterations in the excitability of neurons in the system or a change in connectivity due to a structural rearrangement. Once the hypersensitivity is produced by these activity-independent means it will manifest as a change in the response to stimuli.

changes in the nociceptor terminal environment with both activation of chemosensitive nociceptors and a reduction in transduction threshold (peripheral sensitization), non-activity-dependent alterations in membrane excitability of primary sensory or central neurons due to changes in the expression or localization of ion channels or the removal of central inhibition, and structural reorganization of synaptic connectivity. It is important to distinguish between the mechanisms responsible for producing pain hypersensitivity (which may be independent of any activity) and the established hypersensitivity itself, which may manifest as a change in the response to stimuli.

1.3. Stimulus-generated pain hypersensitivity (Fig. 5)

In contrast, to stimulus-independent hypersensitivity stimulus-generated hypersensitivity represents those situations where the increased pain sensitivity results directly from or is caused by activity in the system elicited by stimuli. This is a manifestation of functional or use-dependent pain plasticity. One clear example of this activity-dependent modifiability of basal sensitivity is C-fiber evoked central sensitization, which can be established in normal individuals. Injection of capsaicin, a C-fiber irritant, into the skin, activates those fibers expressing the VR1 or capsaicin receptor resulting in an intense burst of activity lasting for several minutes. This C-fiber activity is sufficient to induce central sensitization in the spinal cord such that a subsequent tactile and punctate allodynia manifests outside of the area of the capsaicin injection, changes that are due entirely to the increased excitability of the central neurons. Such stimulus-generated pain hypersensitivity is produced in normal individuals only by intense C-fiber activating peripheral stimuli such as capsaicin, mustard oil, or intense heat. After inflammation C-fiber activity is easier to elicit from the periphery, because of the establishment of peripheral sensitization, and spontaneous activity in C-fibers innervating damaged tissue will also drive central sensitization. Alteration in the expression of a variety of centrally acting neuromodulators in C-fibers after inflammation, due to increased production of neuroactive growth factors in the inflamed tissue, may exaggerate their central actions producing a greater degree of central sensitization for the same level of input.

Normally, activation of low threshold mechanoreceptors never produces either pain or elicits pain hypersensitivity. After induction of central sensitization these fibers can directly elicit pain, i.e. tactile allodynia but repeated activation of these fibers in normal individuals does not lead to any central sensitization-like phenomenon. However, after inflammation (and possibly nerve injury), activation of A fibers begins to induce pain hypersensitivity i.e. a change basal pain sensitivity, the phenomenon of progressive tactile hypersensitivity where repeated intermittent light touches to the skin result in the slow build up of a persistent pain hypersensitivity. It is important to recognize that in talking about stimulus-generated pain, stimuli have two very distinct roles. One role is in generating or producing a persistent state of pain hypersensitivity by provoking functional changes in the excitability of neurons in the spinal cord. Another is once the hypersensitivity has been produced, the induced change in basal sensitivity will manifest as an increased response to peripheral stimuli.

Following nerve injury, ectopic activity in injured C-fibers can act as a source of ongoing central sensitization and phenotypic changes in A fibers may make ectopic activity in these afferents also a source for the establishment of central sensitization similar to the progressive tactile hypersensitivity evoked by low intensity stimulation of inflamed skin. The extent to which regenerated fibers after nerve injury or neighboring non-injured fibers change their phenotype and can begin to produce progressive tactile hypersen-

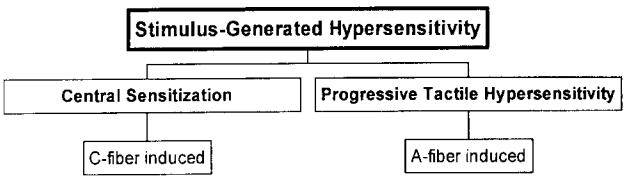

Fig. 5. Stimulus-generated pain hypersensitivity is an activity-dependent or stimulus-evoked change in basal pain sensitivity. This may result from activation of C-fibers leading to central sensitization (which can occur in normal individuals as well as after activation of these fibers in inflammatory conditions or after nerve injury) and from A-fibers, as in progressive tactile hypersensitivity, Activation of A-fibers never normally produces pain nor has the capacity to generate central sensitization. After inflammation (and possibly nerve injury), however, changes in the phenotype of A-fibers gives them capacity to start to produce an increase in central excitability similar to that produced by C-fibers.

sitivity is the subject of ongoing research but preliminary indications from our laboratory are that peripheral stimuli applied to an area of partial denervation may elicit central sensitization. This may mean that stimulus-generated changes in pain sensitivity contribute to neuropathic pain.

1.4. Implications for pain patients

The clinical evaluation of pain currently involves identification or diagnosis of the primary disease/etiological factor considered responsible for producing/initiating the pain, together with placing the patient within a broad pain category, typically nociceptive, inflammatory or neuropathic pain, and identifying the anatomical distribution, quality and intensity of the pain. Sensory testing is usually performed crudely in a manner based on the standard neurological examination with in rare cases, quantitative sensory testing. Treatment is typically based on the broad pain category, with in the case of neuropathic pain, a treatment plan essentially based on trial and error, starting with the current favorite drug of choice, and working ones way down the list, looking for optimal relief and minimal side effects. Mechanism is neither diagnosed nor represents the basis for treatment. We feel this approach needs to be replaced.

Etiological or disease-based clusters include conditions such as post-operative pain, osteoarthritic pain, low back pain, diabetic neuropathy, postherpetic neuralgia or cancer pain, with no consideration as to what mechanisms are responsible for the production of the pain. While there is no doubt that identifying the disease is essential, particularly where disease modifying treatment is required, as in acute herpes zoster, diabetes, or pain due to infiltration by a tumor of a nerve, in the vast majority of patients with persistent (chronic) pain, the disease or pathology cannot be treated and the injury is not reversible. This group of patients includes those with peripheral/segmental nerve lesions of multiple causes, brachial avulsion or spinal cord injury and post-stroke central pain. We believe that it is helpful to consider pain itself as the disease in these cases, and instead of emphasizing or categorizing the patient primarily or exclusively on the diagnosis of the primary disease, an attempt should be made to identify the mechanisms responsible for the pain. This is a very difficult task, not least because not all mechanisms that contribute to pain pathophysiology are known, and even those that have been identified cannot usually be determined in patients, the diagnostic tools are simply not available.

We are limited in the reality of the busy pain clinic to attempting to assess how the pain an individual patient experiences falls within a general schema that may reflect different pain mechanisms. While this is unsatisfactory it is, we strongly believe, preferable to crude global measures of pain such the simple VAS score, rating scales or pain descriptor profiling currently used. There is, moreover, the need for more information about the nature of a patient's pain than can be gleaned from a diagnosis such as postherpetic neuralgia. With this in mind we have attempted to design a qualitative pain assessment profile for use in the clinic based on an analysis of pain, defined by the mechanisms described above. The aim of this approach is to evaluate basal pain sensitivity and its modifications, by eliciting from the patient during an interview, key aspects of the nature of their symptoms. This will require a different sort of clinical pain record, one based on the quality of the pain as reported by the patient, and gleaned by careful indirect questioning, than the usual global assessments. Such an interview-based pain record will supplement, of course, the standard history and physical examination of the patient, including sensory testing to evoke symptoms.

Fig. 6 shows how basal pain sensitivity could be qualitatively assessed in patients, by a selective elicitation of the nature of the symptoms experienced by the patient. This should only require a relatively brief, semi-directed interview, beyond the standard history, but one designed specifically to establish if the patient has normo-, hypo- or hyperbasal pain sensitivity and the extent to which the pain is spontaneous or evoked. Systematic questions need to be posed that enquire about what type and intensity of stimuli evoke pain, the nature of the pain response, its quality, localization, timing, and intensity. For example, in a patient with postherpetic neuralgia, one would aim to determine by such questioning whether the patient has ongoing pain, and if so is it continuous or intermittent, if there is pain on transient contact with clothes, if sustained pressure such as a bra strap causes pain and if cold relieves or exacerbates the pain. Intensity could be rated in a number of ways using VAS scales or rating scales. Quality of pain could be

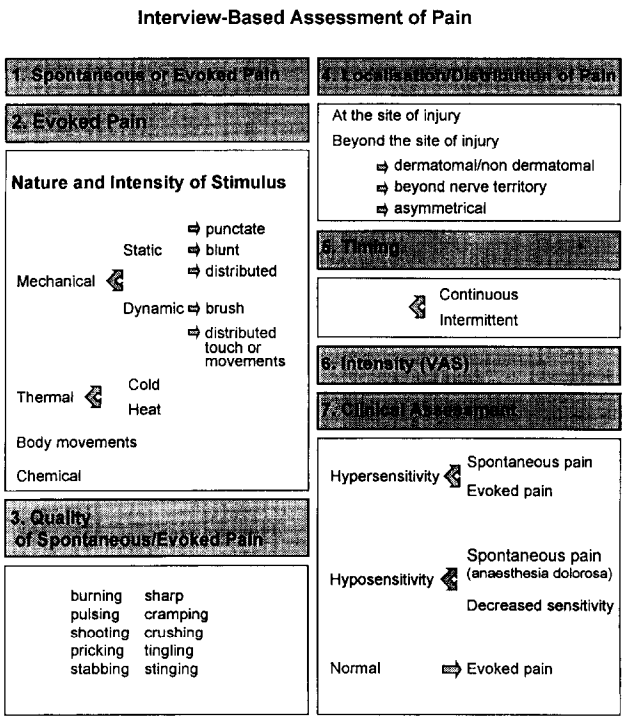

Fig. 6. An interview-based qualitative assessment of pain.

described using those descriptors in the sensory component of the McGill pain questionnaire.

It will be necessary to compare the patient's own report of their pain, established in the interview, with the results obtained by simple sensory tests in the physical examination, using tests aimed to measure the presence and extent and of any abnormal evoked pain sensitivity. It is obviously not ethical to test routinely for the presence of stimulus-evoked pain hypersensitivity in patients. This will need to be evaluated in carefully designed clinical research investigations.

1.5. Implications for evaluation of efficacy of new therapies

A major problem in clinical studies of pain is the high intra and inter patient variability in pain scoring using global outcome measures and hence the enormous difficulty in evaluating the efficacy of novel analgesics (Moore et al., 1999). The usual explanations for the variability are the complexity of pain mechanisms, changes in the primary disease, and psychological factors. We think this is too defeatist and another approach is called for, one that may provide new clinical outcome measures that might enable an evaluation of whether new analgesics have an action on particular mechanisms.

If a new therapy is given to patients selected only on the basis of particular disease e.g. diabetic neuropathy, and the clinical outcome measure is a simple global pain measure, say a VAS score of pain at rest, it is simply not possible to assess whether the treatment is selectively acting on one mechanism (say central sensitization) and reducing a particular symptom like tactile allodynia. Since the degree of central sensitization may differ considerably in this cohort of patients from none to a major determinant of the pain symptomatology, any treatment that acts only on central sensitization will produce highly varied responses across the whole population. We believe that the pain assessment plan we propose may help by breaking pain down into components that reflect some of the major different mechanisms. Such a breakdown may help identify how and why certain treatments work. Of course this approach needs to be validated but its simplicity is, we feel, its strength, increasing its usefulness beyond tertiary referral centers. The extent to which information obtained from such a qualitative assessment compares with results obtained from quantitative sensory testing, will need to be formerly tested. Further insight into the mechanisms of pain enabling more accurate categorization of pain together with the establishment of new diagnostic tools; will greatly increase the efficiency of a mechanism-based pain assessment.

2. Conclusion

The aim of this article has been to highlight some of the advances that have and are being made in how pain is generated and to detail how this progress can be used to begin construct a new approach for assessing pain in patients. Such new clinical analyses are required if we are to embark on more sophisticated investigations of pain epidemiology and treatment.

References

Akopian AN, Sivilotti L, Wood JN. A tetrodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons. Nature 1996;379:257–262.

Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain 1988;33:87–107.

Castro-Lopes JM, Tavares I, Coimbra A. GABA decreases in the spinal cord dorsal horn after peripheral neurectomy. Brain Res 1993;620:287–291.

Chen CC, Akopian AN, Sivilotti L, Colquhoun D, Burnstock G, Wood JN. A P2X purinoceptor expressed by a subset of sensory neurons. Nature 1995;377:428–431.

Devor M, Govrin-Lippman R, Angelides K. Na^+ channel immunolocalization in peripheral mammalian axons and changes following nerve injury and neuroma formation. J Neurosci 1993;135:1976–1992.

Eide PK, Jorum E, Stubhaug A, Bremmes J, Breivik H. Relief of post-herpetic neuralgia with the *N*-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. Pain 1994;58:347–354.

Gold MS, Reichling DB, Schuster MJ, Levine JD. Hyperalgesic agents increase a tetrodotoxin-resistant Na^+ current in nociceptors. Proc Nat Acad Sci USA 1996;93:1108–1112.

Keiffer BL, Befort K, Gaveriaux-Ruff C, Hirth CG. The delta-opioid receptor: Isolation of a cDNA by expression cloning and pharmacological characterization. Proc Nat Acad Sci USA 1992;89:12048–12052.

Kim SH, Chung JM. An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat. Pain 1992;50:355–363.

Koerber HR, Mirnics K, Brown PB, Mendell LM. Central sprouting and functional plasticity of regenerated primary afferents. J Neurosci 1994;14:3655–3671.

Koerber HR, Mimics K, Kavookjian AM, Light AR. Ultrastructural analysis of ectoic synaptic boutons supported by regenerated afferent fibers. Soc Neurosci Abstr 1995;21:566.

Koltzenburg M, Lundberg LER, Torebjork HE. Dynamic and static components of mechanical hyperalgesia in human hairy skin. Pain 1992a;51:207–220.

Koltzenburg M, Wahren LK, Torebjork HE. Dynamic changes of mechanical hyperalgesia in neuropathic pain states and healthy subjects depend on the ongoing activity of unmyelinated nociceptive afferents. Pflugers Arch 1992b;420:R52.

Koltzenburg M, Torebjork HE, Wahren LK. Nociceptor modulated central sensitization causes mechanical hyperalgesia in acute chemogenic and chronic neuropathic pain. Brain 1994;117:579–591.

Ma Q-P, Woolf CJ. Progressive tactile hypersensitivity: an inflammation-induced incremental increase in the excitability of the spinal cord. Pain 1996;67:97–106.

Ma Q-P, Woolf CJ. Morphine, the NMDA receptor antagonist MK801 and the tachykinin NK1 receptor antagonist RP67580 attenuate the development of inflammation-induced progressive tactile hypersensitivity. Pain 1998;77:49–57.

Matthes HWD, Madonada R, Simonin F, Valverde O, Slowe S, Kitchen I, Befort K, Dierich A, LeMeur M, Dolle P, Tzavara E, Hanoune J, Roques BP, Kieffer BL. Loss of morphine-induced analgesia, reward effect and withdrawal symptoms in mice lacking the mu-opioid-receptor gene. Nature 1996;383:819–823.

Mitchell JA, Akarasereenont P, Themermann C, Flower RJ, Vane JR. Selectivity of non-steroidal antiinflammatory drugs are inhibitors of

constitutive and inducible cyclogenase. Proc Nat Acad Sci USA 1993;90:11693–11697.

Moore RA, Gavaghan D, Tramer MR, Collins SL, McQuay H. Size is everything — large amounts of infomation are needed to overcome random effects in estimating direction and magnitude of treatment effects. Pain 1999;78:209–216.

Neumann S, Doubell TP, Leslie TA, Woolf CJ. Inflammatory pain hypersensitivity mediated by phenotypic switch in myelinated primary sensory neurones. Nature 1996;384:360–364.

Noguchi K, Kawai Y, Fukuoka T, Senba E, Miki K. Substance P induced by peripheral nerve injury in primary afferent sensory neurons and its effect on dorsal column nucleus neurons. J Neurosci 1995;15:7633–7643.

Novakovic SD, Tzoumaka E, McGivern JG, Haraguchi M, Sangameswaran L, Gogas KR, Eglen RM, Hunter JC. Distribution of the tetrodotoxin-resistant sodium channel PN3 in rat sensory neurons in normal and neuropathic conditions. J Neurosci 1998;18:2174–2187.

Reeh PW. Chemical excitation and sensitization of nociceptors. In: Urban L, editor. Cellular mechanisms of sensory processing. NATO ASI series, Cell Biology Vol 79. Berlin: Springer-Verlag, 1994. pp. 119–131.

Ren K, Dubner R. Enchanced descending modulation of nociception in rats with persistent hindpaw inflammation. J Neurophysiol 1996;76:3025–3037.

Shortland P, Woolf CJ. Chronic peripheral nerve section results in a rearrangement of the central axonal arborizations of axotomized A beta primary afferent neurons in the rat spinal cord. J Comp Neurol 1993;330:65–82.

Stein C, Millan MJ, Herz A. Unilateral inflammation of the hindpaw in rats as a model of prolonged noxious stimulation: alterations in behavior and nociceptive thresholds. Pharmacol Biochem Behav 1988;31:445–451.

Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A. Mapping of punctuate hyperalgesia around a surgical incision demonstrate that ketamine is a powerful suppressor of central sensitization to pain following surgery. Acta Anaesthesiol Scand 1997;41:1124–1132.

Sugimoto T, Bennett GJ, Kajander KC. Transynaptic degeneration in the superficial dorsal horn after sciatic nerve injury: effects of a chronic constriction injury, transection and strychnine. Pain 1990;42:205–213.

Tate S, Benn S, Hick C, Trezise D, John V, Mannion RJ, Costigan M, Plumpton C, Grose D, Gladwell Z, Kendall G, Dale K, Bountra C, Woolf CJ. Two sodium channels contribute to the TTX-R sodium current in primary sensory neurons. Nature Neurosci 1998;1:653–655.

Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K, Raumann BE, Basbaum AI, Julius D. The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron 1998;21:531–543.

Waldmann R, Champigny G, Bassilana F, Heurteaux C, Lazdunski M. A proton-gated cation channel involved in acid-sensing. Nature 1997;386:173–177.

Willis WD, Coggeshall RE. Sensory mechanisms of the spinal cord, New York: Plenum Press, 1991.

Woolf CJ, Wall PD. Chronic peripheral nerve section diminishes the primary afferent A-fibre mediated inhibition of rat dorsal horn neurones. Brain Res 1982;242:77–85.

Woolf CJ, Shortland P, Coggeshall RE. Peripheral nerve injury triggers central sprouting of myelinated afferents. Nature 1992;355:75–77.

Woolf CJ, Shortland P, Reynolds ML, Ridings J, Doubell TP, Coggeshall RE. Central regenerative sprouting: the reorganization of the central terminals of myelinated primary afferents in the rat dorsal horn following peripheral nerve section or crush. J Comp Neurol 1995;360:121–134.

Woolf CJ, Bennett GJ, Doherty M, Dubner R, Kidd B, Koltzenburg M, Lipton R, Loeser JD, Payne R, Torebjork E. Towards a mechanism-based classification of pain? Pain 1998;77:227–229.

Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature 1983;306:686–688.