Medical Hypotheses (2006) x, xxx–xxx

medical hypotheses

http://intl.elsevierhealth.com/journals/mehy

Chronic pain: A non-use disease

L. Pruimboom *, A.C. van Dam

Faculty of Human Sciences, University of Gerona, C/Francesc Masia 65 Salt, Spain

Received 20 July 2006; accepted 1 August 2006

Summary One of the major problems in modern medicine is to find remedies for the group of people with chronic pain syndromes. Low back pain is one of the most frequent syndromes and perhaps the most invalidating of all of them. Chronic pain seems to develop through several pathways affecting the spinal cord and the brain: (1) neuro-anatomical reorganisation, (2) neuro-physiological changes, and (3) activation of glia cells (immune reaction in the central nervous system). Although all of these pathways seem to provide a (partial) plausible explanation for chronic pain, treatments influencing these pathways often fail to alleviate chronic pain patients. This could be because of the probability that chronic pain develops by all three mechanisms of disease. A treatment influencing just one of these mechanisms can only be partially successful. Other factors that seem to contribute to the development of chronic pain are psychosocial. Fear, attention and anxiety are part of the chronic pain syndrome being cause or consequence. The three pathways and the psycho-emotional factors constitute a psycho-neuro-immunological substrate for chronic pain syndromes; a substrate which resembles the substrate for phantom pain and functional invalidity after stroke. Both phantom pain and functional invalidity are considered non-use syndromes. The similarity of the substrate of both these two neurological disorders and chronic pain makes it reasonable to consider chronic pain a non-use disease (the hypothesis).

To test this hypothesis, we developed a ''paradoxal pain therapy''. A therapy which combines the constraint induced movement therapy and strategies to dissociate pain from conditioning factors like fear, anxiety and attention. The aim of the therapy is to establish a behaviour perpendicular on the pathological pain-behaviour. Clinically, the treatment seems promising, although we just have preliminary results. Further clinical and laboratory studies are needed to measure eventual changes at neuro-anatomical and neuro-psychological level using modern neuro-imaging instruments (PET, SPECT, fMRI). Randomised clinical trials should be carried out to test our hypothesis for all-day use in clinical practice. The hypothesis: chronic pain is a non-use disease produced by psycho-emotional factors like fear, attention and anxiety. Optimal treatment should be based on physiological use, and dissociation of pain and the mentioned psycho-emotional factors. Paradoxal pain therapy could serve these treatment conditions.

Introduction

Finding remedies for patients with chronic pain is one of the most difficult and at the same time one of the most intruding objectives of modern scientific investigation. The last decade has brought a lot of new insides in the mechanisms of disease for

* Corresponding author. Present address: Faculty of Human Sciences, University of Gerona, C/Los Helechos 5a, 35500 Arrecife, Las Palmas, Spain. Tel.: +34 928844959.
E-mail address: leo.pruimboom@fudgif.udg.es (L. Pruimboom).

0306-9877/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.mehy.2006.08.036

Please cite this article in press as: Pruimboom L, van Dam AC, Chronic pain: A non-use disease, Medical Hypotheses (2006), doi:10.1016/j.mehy.2006.08.036

people with chronic pain syndrome. Neurological imaging techniques like positron evoked tomography (PET) and functional MRI (fMRI) have made it possible to visualise changes at neurological, histological and immunological level. Resuming the results of the most revealing work of the last decade [1–3] it seems obvious that mechanisms of disease for developing chronic pain include:

1. Neuro-anatomical reorganisation in the spinal cord and the brain.
2. Neuro-physiological changes in the spinal cord and the brain.
3. Activation of glia cells (immune reaction in the central nervous system).

Craig et al. [2,4] have developed a reasonable amount of evidence that pain is an efferent homeostatic feeling produced as a reaction on labelled line interoceptive afferent information. Interoceptive afferents transport all kind of information related to changes of the homeostasis, ranging from tissue damage to hypoxia and acidosis. The interoceptive afferents enter the spinal cord via lamina I neurons (in the so called heat-pinch-cold neurons), cross to the other side of the spinal cord and ascend as a spinothalamic tract through homeostatic centres in the brain stem and thalamus, ending up in the insular cortex and gyrus cingularis. Their theory is that chronic pain is caused by central sensitisation of the so called ''neuromatrix of homeostasis'' and involves neuro-anatomical and neuro-physiological pathways. For an excellent review of labelled line interoceptive afferents and pain, I would like to refer to [5].

Wieseler-Frank et al. [6,7] describe chronic pain as a process of activation of glia cells in the spinal cord. Glia cells (microglia and astrocytes) normally exhibit minor (astrocytes) or no activity (microglia) in physiological circumstances. Several factors, like long term use of morphine, virus, trauma and ischemia, can activate glia cells (Fig. 1). Once glia

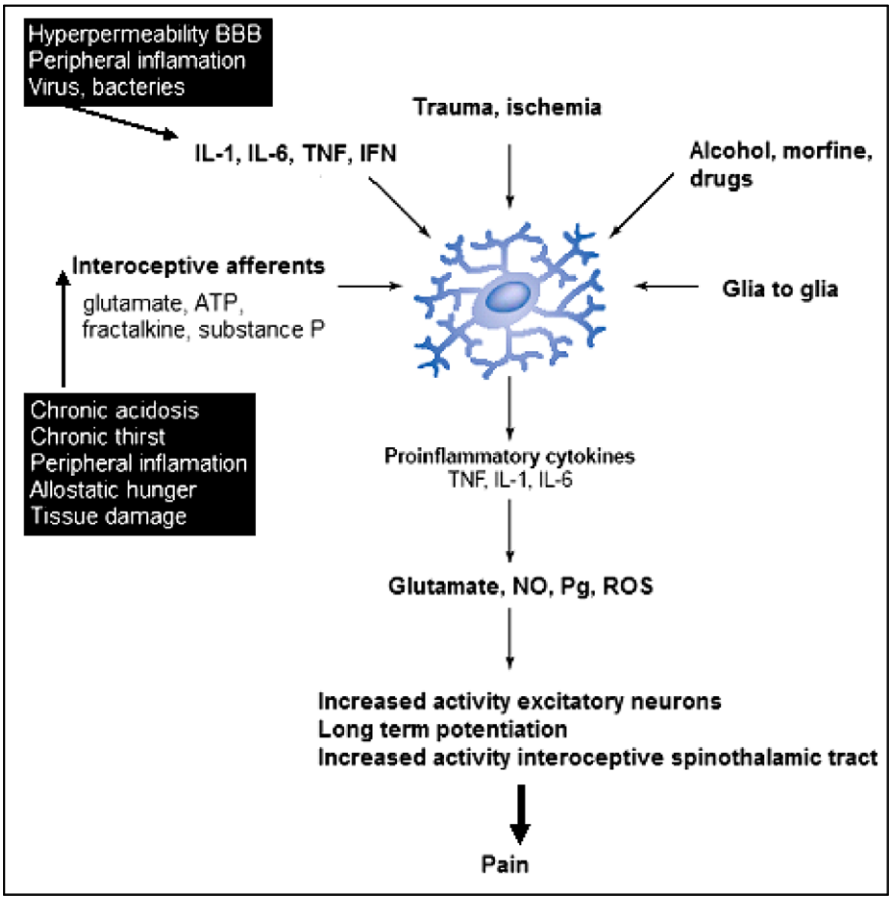

Figure 1 Glia-cell activation as a direct cause for enhanced activity of excitatory neurons in the spinal cord, provoking a pain sensation. Interoceptive afferents can be activated by a great deal of peripheral homeostatic imbalances. All of them can activate glia cells in lamina I of the spinal cord. Glia cell activation can continue with absence of the initial activator.

Please cite this article in press as: Pruimboom L, van Dam AC, Chronic pain: A non-use disease, Medical Hypotheses (2006), doi:10.1016/j.mehy.2006.08.036

cells are activated they produce pro-inflammatory cytokines like interleukin 6 (IL6), interleukin 1 (IL1) and tumor necrosis factor alpha (TNFα). These substances are able to activate excitatory neurons in the spinal cord responsible for afferent pain (interoceptive) transmission. Chronic activation of glia cells can produce long term changes in neuronal activity in spinal cord and brain neurons responsible for pain transmission; changes which could be responsible for the development of chronic pain syndromes.

Results of clinical trials using antagonistic drugs of pro-inflammatory cytokines (glia-modulator) show that these kind of treatments are promising for people with chronic pain syndromes [8–11].

Current treatment of patients with chronic pain syndrome is based on the neuro-immunological pathways of developing chronic pain. Tricyclic antidepressants [12,13], gabapentin and morphine [14] are the most frequently used drugs combined with anti-inflammatory drugs (NSAID), glia-modulator drugs and cognitive psychotherapy. Effectiveness of these treatments has been proven, although there still is a group of non-reacting patients, and secondary effects of pain-drugs are considerable.

For these reasons we have developed a new therapy for patients with chronic pain based on the similarity of the scientific substrate of both phantom pain and chronic pain [15,16]. Phantom pain is considered a non-use syndrome. If chronic pain patients present a similar substrate as patients with non-use syndromes, than chronic pain could also be considered a non-use syndrome. If so then:

First	Chronic pain patients should hardly use there affected part of the body;
Second	Constraint induced use of the affected part of their body should change the pain intensity and function and;
Third	Deep learning and massive training of the affected part of the body should provide a re-reorganisation of neuro-anatomical structure in the brain and spinal cord. Neuro-physiological changes should include neurotransmitters and glia-cell activation.

The theory

People with chronic pain tend to ''fly'' from their affected part of the body. Fear for pain and more damage seems to be the mayor reason for this part of the typical pain-behaviour [17–20]. Other pain-behaviour characteristics are anxiety and continuous focusing on the pain. Fear, anxiety and chronic focusing can be considered ''homeostatic feeling''. All these homeostatic feeling activate the so called interoceptive cortex (insular cortex) and the gyrus cingularis [4,5]. When fear, anxiety, pain and pain-focusing activate the interoceptive cortex at the same time, in the end they will be neurologically connected:

''When two neurons fire together they wire together and if they don't they won't''

The described process of classical and operant conditioning will lead to the typical neuro-psychological substrate for chronic pain patients:

There is no pain without fear [21];
There is no pain without anxiety [21];
There is no pain without attention [22] and;
There is no pain without gain [21].

This pain-behaviour reduces the use of the affected area. Reduced or non-use of a part of the body results in a neuro-anatomical reorganisation in various parts of the brain [15,23]; a situation similar to patients with phantom pain. Patients with phantom pain are successfully treated with constraint induced movement [(CIMT,15,23)]. A therapy based on limitation of the non-affected side of the body and massive use (6 h a day) of a functional prosthesis adapted to the amputated extremity.

''Paradoxal pain therapy'' is based on a combination of CIMT and dissociation-techniques of neuronal connections.

The hypothesis

Chronic pain is a non-use disease provoked by psycho-emotional factors like fear, attention and anxiety [25]. Treatment should be based on 1. physiological use, and 2. on dissociation of pain and the mentioned psycho-emotional factors. ''Paradoxal pain therapy'' could serve these treatment conditions.

Paradoxal pain therapy

1. Deep learning therapy.
2. Dissociation-techniques Inform the environment to ''forget'' the pain of the affected patient. Pain-associated behaviour of the patient is not rewarded anymore (loss of gain and attention).

Please cite this article in press as: Pruimboom L, van Dam AC, Chronic pain: A non-use disease, Medical Hypotheses (2006), doi:10.1016/j.mehy.2006.08.036

3. Constraint induced use of affected area (from fearful non-use to relaxed massive use).
4. Illusion technique as an early pain-distraction strategy.

Ad. 1. Patients are informed about the influence of emotions (fear, anxiety) and attention on their pain syndrome. Further information is given about the pathways that lead to the neuro-immunological changes in the spinal cord and brain [24]. It is important to state that the patient's problem is not a psychological but a neurological problem. The profound explanation (deep learning) activates motivational areas in the brain; areas which belong to the so called central reward circuit [25]. Several parts of the central reward circuit are able to produce a serial of pain-inhibiting neurotransmitters like endorphins, dopamine and GABA. Activation of these areas by deep learning enhances pain-killing processes and diminishes fear and anxiety by rational understanding of the pain process. Deep learning explanation has to be profound and understandable for every individual and includes neuro-physiological, neuro-anatomical and psycho-emotional pathways related with chronic pain.

Ad. 2. Patient and the direct environment are informed about the influence of attention related to pain and pain-behaviour. Pain-behaviour should be avoided (for instance, hand supporting the low back in patients with chronic low back pain) by the patient and ignored by his/her environment.

Ad. 3. Patient trains her/his affected part of the body using a massive training program of difficult motor tasks, constraining other parts of the body. The therapist can help to execute the tasks if necessary. Before starting the program the therapist valorises the actual functions of the patient. After inventorying the different tasks, training begins. The amount of repetitions depends on resistance declared by the patient. This means that the patient and the therapist choose respectively, the intensity of training and the task. A training session lasts not more than 60–90 min. The constraint part of the body has to be constraint for at least 50% of wakeful daytime.

Hence, these conditions for constraint induced movement training in patients with chronic pain vary compared with the CIMT for patients with phantom pain or stroke. The adaptation is based on the fact that the affected part of the body is still there and tissue overload has to be avoided. Studies of Moseley [24] made it clear that overload can be prevented if the patient chooses intensity (load, the number of repetitions, pause between the repetitions and the context in which the task is executed). The CIMT period duration in chronic pain patients varies from 8 days to 14 days. After one month a new training program starts (if necessary) adapted to the actual functions of the patient. Task difficulty depends on function and not on pain. Task may not provoke fear or anxiety.

Restoration of function is probably the missing link treating patients with chronic pain. Current cognitive/behavioural- and medical therapies to often focus on pain killing alone [26]. The CIMT recovers normal function, offering physiological information to the brain areas responsible for interoceptive/homeostatic analysis. These areas can produce the homeostatic feeling ''pain'' but would not do so if the information, which enters these areas is completely normal.

Ad. 4. Patients with chronic pain often (almost always) start a new day focusing on their pain. ''How will I feel today? Will I be in agony? This means that although they feel no pain at that moment, their brain (and spinal cord) is already occupied with pain and fear for pain. To prevent this focusing moment (with a huge impact on pain-conditioning processes) at the beginning of the day, patients have to carry out a so called ''illusion therapy''. This therapy (therapy conditions see frame) has proven its effects in laboratory investigations of patients with pain in our clinic. Effects seem to be mediated by changes in endorphin and dopamine production in the reward circuit of the brain. Both natural neurotransmitters are able to regulate neurological activation in pain transmission neurons [27]. Another goal is to distract patient's attention to the pain, being distraction-therapy one of the most promising treatments for chronic pain patients [28–30].

Please cite this article in press as: Pruimboom L, van Dam AC, Chronic pain: A non-use disease, Medical Hypotheses (2006), doi:10.1016/j.mehy.2006.08.036

Illusion therapy

When you wake up in the morning you plan on doing something you like (for instance; today I go to the cinema). Planning includes time (at eight p.m.) and capability of execution. At last you have to carry out your plan.
Frequency 5 times a week
The same wish can't be repeated more than 5 times a month (to prevent adaptation).

Discussion and conclusion

Scientific research in the last decades has brought a lot of new insides in the treatment of patients suffering chronic pain syndromes. Current treatments include morphine, tricyclic antidepressants, anti-inflammatory drugs and cognitive psychotherapy with acceptable results. However side-effects are considerable and rebound effects (more pain after a period of treatment) are frequent. A further problem is that normal function is not recuperated. The mentioned therapies are based upon current knowledge about neurological, immunological and physiological processes related to chronic pain syndromes. The theory of our hypothesis is based upon the same processes; people suffering chronic pain present changes on neurological, immunological and physiological levels, which give a plausible explanation for the persistence of their pain. These changes seem to be produced by chronic activity of interoceptive afferents combined with pain-focusing and conditioning feelings like fear and anxiety. The ultimate consequence is a lack of use of the affected part of the body. We think that an optimal therapy for chronic pain patients should include massive use of the affected part of the body, eliminating at the same time the conditioning feeling; leading to a normalisation of activity and anatomy of the spinal cord and affected areas in the patient's brain. Paradoxal pain therapy could fit these treatment conditions, although laboratory and clinical research has to approve its value in all day clinical practice.

References

[1] Watkins LR et al. Glia: novel counter-regulators of opioid analgesia. Trends Neurosci 2005;28(12):661–9.
[2] Craig AD. How do you feel? interoception: the sense of the physiological condition of the body. Nat Rev Neurosci 2002;3(8):655–66.
[3] Taub E et al. A placebo-controlled trial of constraint-induced movement therapy for upper extremity after stroke. Stroke 2006;37(4):1045–9.
[4] Craig AD. Pain mechanisms: labeled lines versus convergence in central processing. Annu Rev Neurosci 2003;26:1–30.
[5] Craig AD. Lamina I, but not lamina V, spinothalamic neurons exhibit responses that correspond with burning pain. J Neurophysiol 2004;92(4):2604–9.
[6] Wieseler-Frank J, Maier SF, Watkins LR. Central proinflammatory cytokines and pain enhancement. Neurosignals 2005;14(4):166–74.
[7] Wieseler-Frank J, Maier SF, Watkins LR. Immune-to-brain communication dynamically modulates pain: physiological and pathological consequences. Brain Behav Immun 2005;19(2):104–11;
Cami J, Farre M. Drug addiction. New Engl J Med 2003;349(10):975–86.
[8] Raghavendra V et al. Anti-hyperalgesic and morphine-sparing actions of propentofylline following peripheral nerve injury in rats: mechanistic implications of spinal glia and proinflammatory cytokines. Pain 2003;104(3):655–64.
[9] Raghavendra V, Tanga FY, DeLeo JA. Attenuation of morphine tolerance, withdrawal-induced hyperalgesia, and associated spinal inflammatory immune responses by propentofylline in rats. Neuropsychopharmacol 2004;29(2):327–34.
[10] Dorazil-Dudzik M et al. The effects of local pentoxifylline and propentofylline treatment on formalin-induced pain and tumor necrosis factor-alpha messenger RNA levels in the inflamed tissue of the rat paw. Anesth Analg 2004;98(6):1566–73. Table of contents.
[11] Brooks JC et al. Somatotopic organisation of the human insula to painful heat studied with high resolution functional imaging. Neuroimage 2005;27(1):201–9.
[12] Raja SN et al. Opioids versus antidepressants in postherpetic neuralgia: a randomised, placebo-controlled trial. Neurology 2002;59(7):1015–21.
[13] Max MB. Treatment of post-herpetic neuralgia: antidepressants. Ann Neurol 1994;35:S50–3.
[14] Gilron I et al. Morphine, gabapentin, or their combination for neuropathic pain. New Engl J Med 2005;352(13):1324–34.
[15] Mark VW, Taub E. Constraint-induced movement therapy for chronic stroke hemiparesis and other disabilities. Restor Neurol Neuros 2004;22(3–5):317–36.
[16] Taub E, Uswatte G, Pidikiti R. Constraint-induced movement therapy: a new family of techniques with broad application to physical rehabilitation – a clinical review. J Rehabil Res Dev 1999;36(3):237–51.
[17] Poiraudeau S et al. Fear-avoidance beliefs about back pain in patients with subacute low back pain. Pain 2006.
[18] Grotle M, Vollestad NK, Brox JI. Clinical course and impact of fear-avoidance beliefs in low back pain: prospective cohort study of acute and chronic low back pain: II. Spine 2006;31(9):1038–46.
[19] Boersma K, Linton SJ. Expectancy, fear and pain in the prediction of chronic pain and disability: a prospective analysis. Eur J Pain 2006;10(6):551–7.
[20] Boersma K, Linton SJ. Psychological processes underlying the development of a chronic pain problem: a prospective study of the relationship between profiles of psychological variables in the fear-avoidance model and disability. Clin J Pain 2006;22(2):160–6.
[21] Gifford L. Acute low cervical nerve root conditions: symptom presentations and pathobiological reasoning. Manual Ther 2001;6(2):106–15.
[22] Walker LS et al. Parent attention versus distraction: impact on symptom complaints by children with and

Please cite this article in press as: Pruimboom L, van Dam AC, Chronic pain: A non-use disease, Medical Hypotheses (2006), doi:10.1016/j.mehy.2006.08.036

without chronic functional abdominal pain. Pain 2006;122(1—2):43—52.
[23] Elbert T, Rockstroh B. Reorganisation of human cerebral cortex: the range of changes following use and injury. Neuroscientist 2004;10(2):129—41.
[24] Moseley GL. A pain neuromatrix approach to patients with chronic pain. Manual Ther 2003;8(3):130—40.
[25] Berrendero F et al. Nicotine-induced antinociception, rewarding effects, and physical dependence are decreased in mice lacking the preproenkephalin gene. J Neurosci 2005;25(5):1103—12.
[26] Schofferman J. Restoration of function: The missing link in pain medicine? Pain Med 2006;7(Suppl. 1): S159—65.
[27] Cami J, Farre M. Drug addiction. New Engl J Med 2003;349(10):975—86.
[28] Magora F et al. Virtual reality immersion method of distraction to control experimental ischemic pain. Israel Med Assoc J 2006;8(4):261—5.
[29] Hoffman HG. Virtual-reality therapy. Sci Am 2004;291(2): 58—65.
[30] Jensen S. Back pain-clinical assessment. Aust Fam Physician 2004;33(6):393—5. 397—401.

Please cite this article in press as: Pruimboom L, van Dam AC, Chronic pain: A non-use disease, Medical Hypotheses (2006), doi:10.1016/j.mehy.2006.08.036