MECHANISMS OF PAIN IN ARTHRITIS

RESEARCH STRATEGY MEETING REPORT

29th & 30th November 2007

Chancellor’s Conference Centre, University of Manchester
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SUMMARY

The UK Arthritis Research Campaign (arc) held a research strategy workshop on November 16th and 17th with the aim of identifying priorities for research on the role of complementary therapies in musculoskeletal diseases. Over 20 clinicians and scientists attended with expertise in the methodology of investigating complementary therapies (referred to as CAM), as well as specific expertise in areas such as osteopathy and acupuncture and health service researchers. The programme for the meeting is attached (Appendix 1: Programme).

SESSION I: PAIN AND ARTHRITIS

ANIMAL MODELS OF PAIN

Stuart Bevan, Wolfson Centre for Age-related Research Kings College, London

The majority of our knowledge about the transduction, transmission and modulation of nociceptive signals and pain has been gained by studies in animals. Early studies used primarily acute pain models and measured withdrawal responses to noxious heat (hot plate, tail flick) or mechanical pressure either in naïve animals or shortly after inducing inflammation. These models have been used extensively and successfully to discover and develop various opiate and non-steroidal anti-inflammatory drugs, including the most recent development of cyclo-oxygenase 2 (COX-2) specific inhibitors.

Chronic pain models

During the last 20 years much effort has been focused on the mechanisms of chronic pain, largely driven by the introduction of nerve injury models of neuropathic pain. Acute pain usually serves a protective function. Chronic pain can result from either ongoing tissue pathology or a maladaptation triggered by a prior neuronal insult that does not provide any protective benefits. In such states the neurons can be hypersensitive to mechanical, thermal or chemical stimuli and transmit painful signals in the absence of a noxious stimulus.

Some experimental animal models such as injection of Complete Freund’s Adjuvant or Carrageenan mimic inflammatory pain and have a good track record in predicting the effectiveness of compounds as analgesic or anti-hyperalgesic agents. More emphasis has probably been placed on the study of nerve injury models of neuropathic pain as this clinical condition is recognized as an area of high unmet medical need. Other recent developments have seen the introduction of animal models of cancer (notably bone cancer) pain, diabetic neuropathy, chemotherapy- and HIV-induced pain.

The major uses of chronic pain models have been:

1) To identify and understand mechanisms that may be responsible for chronic pain
2) To identify molecular targets or sites for therapeutic intervention
3) To investigate likely roles of these targets/mechanisms by disrupting the system with drugs (including tool compounds), antibodies, genetic manipulation or RNA interference. The models have also been used to investigate the potential utility of various treatments and to compare the efficacy of one treatment with another.

Animal models have given us important insights into the types of changes that can occur in chronic pain states. The models demonstrate various hypersensitivities to mechanical (mechanical hyperalgesia & allodynia) and thermal (heat hyperalgesia & cold allodynia) stimuli as well as sensitization to some chemical stimuli. The attraction of these models is that the spectrum of symptoms resembles that seen clinically. From these studies we have learned that
Mechanisms of pain in arthritis

Hypersensitivities involve changes in both the peripheral and central nervous systems and that some mechanisms are mediated by activities in non-neuronal cells. Hypersensitivities are associated with altered excitability, which is driven by changes in the phenotype of neurons (and non-neuronal cells) with either increased or decreased expression of key proteins, post-translational protein modifications and alterations in neuronal connectivity. Given the multitude of changes that have been described, the challenge is to identify key events that are critical for the development and maintenance of chronic pain in humans.

The majority of nociception measured in animal models is evoked by mechanical or thermal stimuli. Thermal sensitivities (heat or cold) are usually measured from the latency to withdrawal of the stimulated limb. Mechanical hypersensitivities can be measured by paw pressure thresholds (mechanical hyperalgesia), von Frey hair thresholds (static mechanical allodynia) and latencies for removal from a brush stimulus (dynamic mechanical allodynia). Other types of mechanical stimuli include withdrawal pressure thresholds to joint compression and withdrawal or vocalization when the joint is extended.

Mechanical hypersensitivity in an affected hind limb can also be estimated by measuring the distribution of weight borne between the two hind limbs or by analysis of gait in ambulatory animals. We have little information on spontaneous pain levels although measurements of mobility (telemetry or activity cages) and foot posture (raised paw) may provide some indication of the degree of ongoing, spontaneous pain as well as the pain evoked when the affected limb touches a surface.

Models of joint pain

Many structural models of osteoarthritis (OA) have been developed including spontaneous arthritis in specific strains (mice & guinea pigs), genetically modified animals, surgical models (meniscectomy, anterior cruciate ligament section) and chemical models such as monoiodoacetate (MIA). Surprisingly few studies have investigated whether the observed structural changes are accompanied by pain. Pain has been best studied in the MIA and meniscectomy models with most publications focusing on the MIA model. MIA inhibits glycolysis in chondrocytes (and other cells) and produces a reproducible series of structural changes that mimic some of the events seen in human OA including chondrocyte death, cartilage erosion, separation of necrotic cartilage from underlying bone, exposure of subchondral bone and the sensory neurons in bone, osteolysis and swelling, a reduction in bone mineral content and density and the formation of osteophytes.

The pain behaviours in the MIA model have been compared with those occurring in the menisectomy model. The MIA model shows a sustained difference in hind limb weight bearing over more than a month whereas the meniscectomy model shows an initial difference that resolves over 4 weeks. Both the MIA and meniscectomy models develop a mechanical allodynia (von Frey thresholds) in the adjacent paw but mechanical hyperalgesia (paw pressure threshold) is only seen in the MIA model.

A pharmacological approach has been used to validate the MIA model and the profile resembles the effectiveness of drugs in clinical use. Both paracetamol and an NSAID (diclofenac) reverse the early referred hyperalgesia suggesting an initial inflammatory phase, Gabapentin reduces mechanical allodynia and morphine reverses both the weight bearing difference and referred mechanical allodynia.

Our preliminary studies with the anterior cruciate ligament section model have shown that the weight bearing difference resolves with time and is not affected by morphine or diclofenac. These findings raise the possibility that the behavioural effects reflect joint instability rather than pain.

Other treatments have been used to model inflammatory mono-arthritic pain. Probably the best studied of these is a monoarthritis model evoked by injection of complete Freund’s adjuvant (CFA) into a single joint. This model has been well characterized in rats where the pain behaviours last from days to weeks depending on the dose of CFA injected into the joint. Multiple injections of CFA into the joint are required to elicit long term effects in mice. The model is characterized by joint inflammation, cartilage erosion/destruction and some bone resorption/destruction. These structural changes are associated with an initial joint swelling, which is evident for the first 30 days and then resolves,
and a weight bearing difference that is maintained for over 90 days. In this model, morphine, Ibuprofen, Etirocoxib and dexamethasone reverse the weight bearing difference at both short (14-16 days) and long times (55-59 days) after induction. Other models of mono-arthritis include injection of zymosan, kaolin/carrageenan or carrageenan alone into a joint. Pain behaviours have not been as extensively studied in these models as in the CFA model.

One of the major advances, facilitated by studies using the animal models, is the knowledge that chronic pain states are associated with fundamental and long-lasting changes in the phenotypes and activities of neuronal and non-neuronal cells both in the periphery and in the central nervous system. Some of these changes are known to have clinical correlates. For example, some changes in sensory nerve phenotypes first noted in nerve injury models of chronic pain were subsequently shown to occur in human diseases. There is also evidence that chronic pain is usually driven by an inappropriate input of signals from the peripheral nerves. It is probable that similar changes in neuronal phenotypes and properties occur in chronic joint pain although the specific modifications may well differ from those seen in other types of chronic pain.

The value of animal models

Although animal models have provided much valuable information about, and insights into, pain mechanisms, it is worthwhile to consider their strengths and weaknesses. A valid pain model should bear a close relationship to the human disease and be able to predict the outcome of a novel therapeutic intervention. For pragmatic reasons the models benefit from being robust, readily reproducible and easy to use so that they allow a high throughput of studies. They should provide mechanistic insight and allow genetic accessibility. The inflammatory pain models meet many of these criteria and did predict the clinical efficacy of COX-2 inhibitors. The nerve injury models of neuropathic pain have been disappointing in predicting the efficacy of drugs with completely new mechanisms of action and it is important to address the possible reasons for this lack of success.

- Firstly, relatively few clinical trials have really tested the validity of the animal models. There have only been a few compounds, notably the NK1 receptor antagonists, where the failure in a clinical trial can be unequivocally ascribed to a lack of efficacy. In other cases, the lack of efficacy in the clinical trial may have been due to other factors such as the pharmacokinetics of the compound, side effects or the doses tested.

- Secondly, an important lesson is the need to match the animal model as closely as possible to the human disorder. For example, although nerve injury models mimic many of the symptoms observed in chronic neuropathic pain, the underlying patho-mechanisms after nerve injury probably differ from those operating in the post-herpetic neuralgia and diabetic neuropathy patients in the clinical trials. Neuropathic pain also has multiple aetiologies with a range of underlying mechanisms that will vary in importance in different clinical conditions. There is a need for more ‘translational’ models that match the aetiology of pain in the models and in humans. Potentially better models do exist for neuropathic pain such as chemotherapy (taxol, vincristine) induced pain, which is induced by the same agents in animals and cancer patients. The animal model of streptozotocin-induced diabetes and diabetic pain may also prove to be more predictive of clinical outcomes in diabetic neuropathy patients than the nerve injury models.

These experiences of neuropathic pain models raise questions about the current models of joint pain. Are they likely to be good models? The MIA and chronic CFA models mimic many structural changes seen in different forms of arthritis. On this basis the models are very likely to show neuronal and other changes that can occur in humans with similar structural damage. Clinically used drugs have similar analgesic/ anti-hyperalgesic profiles in the MIA model of joint pain and in osteoarthritis patients. However, we will not know whether the new models of joint pain are predictive of clinical outcomes until novel therapies developed on the basis of efficacy in the animal models are tested in humans. Nevertheless, these models will undoubtedly provide important insights into the potential mechanisms responsible for joint pain and will allow us to identify novel sites for intervention and potential therapy.
**DISCUSSION**

1. There is a continuing debate about the value of animal models for studying human pain and the appropriateness of these models
2. There is for example both greater heterogeneity in human pain and also redundancy within the pain processing pathways
3. Animal models do not reflect the continuous pain seen in human arthritis and animal models do not reflect the typical situation of ageing in regards to human arthritic pain
4. However there are newer animal models available and they are worth testing, for example, with drugs that did not work with older models
5. Animal models also need to consider that what is considered chronic pain is really recurrent acute pain

**RHEUMATOID ARTHRITIS**

*Marzia Malcangio, Neurorestoration Group, Wolfson Centre for Age Related Diseases, King’s College London*

**Introduction**

Rheumatoid arthritis (RA) is an autoimmune chronic inflammatory disease that mainly affects the synovial membrane, cartilage and the bone thereby causing joint destruction and severe pain. Some neurological features of RA can contribute to disability as well as pain symptoms. There are two main treatment strategies for RA:

- Firstly, anti-rheumatic drugs are prescribed in early stage and activity of the disease
- Secondly, in the late stages the joint destruction and secondary osteoarthritis are treated with disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate and gold salts, corticosteroids, cytokine antagonists

Severe, chronic pain in RA patients is a serious clinical problem which greatly impacts the quality of life for these patients. Inflammation is thought to be the major cause of pain although a minority of RA patients develop peripheral neuropathies.

Pain relief in RA is obtained with analgesics such as NSAIDs at doses lower than those required to suppress inflammation (Scott, 2005). Gastrointestinal toxicity is a serious adverse effect of this class of drugs which has been circumvented by the development of the coxibs (COX-2 selective inhibitors). However, the benefits of the coxibs have been outweighed by their potential toxicity, notably increases in cardiovascular adverse events (Scott, 2005). The problems with current analgesics, lack of efficacy and toxicity, highlights the need for new analgesic therapies of RA pain and greater understanding of the molecular mechanisms underlying arthritic pain. In vivo model research is essential for reproducing the pathophysiological environment of RA joints which is likely to be associated with immune signalling pathways distinct from those which can be optimised in ex vivo systems. Although testing hypotheses in preclinical settings is crucial, it remains challenging as the choice of targets for analgesics would be best guided by an analysis of the mechanisms involved in RA pathogenesis which may contribute to the development of chronic pain.

**Animal models of pain in inflammatory pain arthritis**

The current pre-clinical models of joint pain rely upon the injection of an inflammogen in the joint or injection of Freund’s adjuvant in joint/hindpaw to produce unilateral arthritis. In behavioural studies knee joint pain associated with arthritis is measured by weight bearing, gait analysis, spontaneous mobility, paw thresholds to von Frey and heat. It is desirable for such models to be complemented by models that closer mimic the complexity and chronicity of RA such as collagen-induced arthritis (CIA). In this model animals are immunised with heterologous type II collagen in...
Freund’s adjuvant and they develop clinical signs of arthritis such as paw swelling, joint rigidity and sustained T cell responses to the collagen. CIA, which is being used by drug discovery teams for investigating the anti-arthritic activity of anti-inflammatory and disease-modifying drugs, has successfully predicted the beneficial effect of anti-TNF therapy. It is only very recently that thermal and mechanical hyperalgesia have been described in CIA in after the onset of arthritis (Inglis et al., 2007) suggesting that the model is suitable for pain studies. In addition the CIA model is associated with more long-lasting pain behaviours than the CFA model.

**Role of Inflammatory Mediators in Pain**

Several preclinical studies of pain in RA have determined the contribution of inflammatory mediators to sensitising the peripheral endings of sensory neurons in arthritic joints. However, as the multiple mediators of pain and inflammation are products of injury-induced gene expression which lead to plastic changes in the nervous system and immune responses, more investigations on central changes in spinal cord and brain might provide novel drug targets for RA pain.

The cytokines are classical targets for RA because they are implicated in both initial and late phases in the arthritic joint and extracellularly regulate both immune and inflammatory responses. Therapeutic blockade of TNF yields clinical response in 70% of patients with established RA and it is most effective early in disease. TNF and IL-1 are found in the synovial fluid and they can directly sensitise nociceptive neurons at their peripheral terminals within the joint through the activation of IL-1- and TNF- receptors which are expressed by sensory neurons.

**P38 MAP kinase inhibitors**

In order to develop orally available treatments for RA some effort has been put in the development of p38 mitogen activated protein (MAP) kinase pathway inhibitors thereby downregulating the production of cytokines (Adams et al., 2001). Encouraging pre-clinical studies show that P38 inhibitors reverse allodynia and hyperalgesia in the CFA model of inflammation (Ji et al., 2007).

**Role of Spinal microglial cells and astrocytes**

Chronic pain results from the persistence of the mechanisms activated by tissue injury and growing evidence shows that microglial cells and astrocytes become activated in the spinal cord following peripheral insults and these cells release inflammatory mediators which modulate neuronal mechanisms in the CNS (Wieseler-Frank et al., 2005). It is like the CNS becoming the mirror image of the periphery. However, the extent of activated microglial and astroglial cells contribution to arthritic pain and our understanding of glial–neuronal and glial-glial communication in the spinal cord that leads to persistent inflammatory pain are still limited. Furthermore, in model systems of arthritis associated with a sustained T cell response, it remains to be established whether these cells infiltrate the spinal cord and contribute to pain mechanisms by releasing old and/or new cytokines such as the IL-17. Intriguingly, in models of neuropathic pain following peripheral nerve injury IL-17 expression has been found in degenerating peripheral nerves. Furthermore, mice lacking functional T cells develop less severe hyperalgesia after nerve injury (Kleinschnitz, 2006).

The physiological relevance of glial inhibition as a therapeutic target for chronic pain awaits validation in humans. However, drugs targeting glial cells may add analgesic efficacy to traditional analgesic drugs. The redundancy of pain signalling makes it unlikely that there is a universal analgesic that can intrinsically reduce all forms of pain. This suggests that targeting multiple molecules and receptors involved in pain and inflammation might be a valid approach. Such an ambitious proposal would benefit from the development of research consortia to identify critical targets for pain research in RA.

**References**

Mechanisms of pain in arthritis


OSTEOARTHRITIS

Dr. Candy McCabe, Royal National Hospital for Rheumatic Diseases & School for Health, University of Bath

Background

Increasing pain and stiffness of the joints is something that is widely regarded as a natural consequence of ageing and many of these problems can be attributed to Osteoarthritis (OA) which is the leading cause of joint pain and disability in older adults (1,2). OA may affect any synovial joint but commonly occurs in the knees, hips, hands and spine with most people over the age of 70 years having some of their joints affected (1,3). Pain in OA is typified by the sufferer describing stiffness on initial movement, increasing pain with prolonged movement and disturbed sleep due to pain (4). There is a reduction in the range of movement in the affected joint and associated muscle weakness.

Research to date, on the generation and perpetuation of OA and pain, has focused on the individual structures of the synovial joint and the role these structures and the biochemical pathways that serve them, may play (see 5 for overview). However, there is not a close correlation between the degree of structural damage and the level of reported pain (6,7) which suggests other mechanisms may contribute to OA pain. It is the developing work on the role of the sensorimotor system in the generation of pain that may help us to understand how high levels of pain may be reported in the absence of significant radiographic changes in OA.

What are the key recent findings that should inform future research?

Imaging studies have shown that when there is a conflict between motor output and predicted sensory feedback there is increased activity in the right dorsolateral pre-frontal and parietal cortices (8). These areas are known to be active during complex motor tasks (9) and those that require increased motor effort (10). Furthermore, when such a conflict is artificially induced in healthy volunteers, via manipulation of sensory feedback with a mirror, 66% (n = 27) of subjects performing bilateral limb movements described sensory disturbances, including pain and stiffness, in the hidden limb (11). Individual vulnerability to such sensory changes was demonstrated with some individuals experiencing no problems whilst others reported a wide range of sensations that they considered were distressing. In addition, increasing age and pre-existing chronic pain appears to amplify a subject’s vulnerability to the generation of these symptoms (12). These findings would appear to confirm Harris’ hypothesis that the pain reported in a number of chronic conditions (e.g. phantom limb pain, chronic low back pain) arises from a mismatch between motor output and sensory feedback (13). In addition, it gives further evidence to previous studies that the sensation of stiffness may be centrally generated and arise from irregularities within the motor control system (14).

Role for proprioception

It is known that proprioception reduces with age and with OA (15). In OA knee it has been demonstrated that this reduction in proprioception occurs in the affected and contra-lateral knee joint and that such a reduction may indeed predispose an individual to the onset of OA (16). Furthermore, joints located at a distance from the knee also...
demonstrate a reduction in proprioception (17) thereby suggesting that problems with the motor control system are not confined to the affected area alone but may be more widely present. Interestingly, the loss or reduction of one sense is known to have a negative effect on multi-sensory integration that is required for effective spatial integration (18,19) and perhaps this makes the ageing adult more vulnerable to the onset of changes in motor sensory integration and ultimately OA? The range in patient reported pain in OA may be more related to the individual vulnerability to cortically derived pain from changes in the motor control system than directly related to the structural changes within a joint. However, once these structural changes do occur one could imagine this would maintain and perpetuate the problems with proprioception and so the cycle would continue.

Therapies that have been devised to correct this sensorimotor incongruence in other chronic pain conditions have proved to give enhanced motor control and analgesic benefit (20-24). They have been designed to target all stages of motor planning progression from enhancement of pre-motor planning to the provision of corrective sensory feedback but to date the studies have been small and there is little long term follow up data. In OA, increasing emphasis is being given to exercise based therapies which may be working through enhanced proprioception (25, 26).

Key objectives of future research

It needs to be established what role this newly defined cortical model of pain has in the generation and/or the perpetuation of pain related symptoms in OA. It may indeed also play a part in the pathogenesis and/or progression of the disease. Work to date in other chronic pain conditions has approached this from a number of different angles and this may be a sensible model to follow in OA. Clinical studies have been designed to identify any pre-existing motor sensory mismatch and test the efficacy of novel therapies created to correct this discrepancy. Some of these studies have been supported by imaging techniques and others have relied on detailed histories and qualitative descriptors. Both designs appear to contribute equally valuable data. Highly sophisticated imaging studies have been used to look in detail at the movement trajectory of a single limb and identify at what point problems may arise and others have focused on changes within the motor and sensory cortices. More laboratory based work has studied the impact of such a discrepancy on other key body systems such as the autonomic and immune systems. This may also be relevant in OA. Finally, once common characteristics are identified it would be helpful to identify those individuals who are at greatest risk of developing a sensorimotor discrepancy so that interventions may be put in place early to reduce or prevent the disabling consequences of OA. Clearly a multi-disciplinary and multi-specialty approach to this work would be optimum.

References


DISC DISEASE

Tony Freemont, Head of Osteoarticular Pathology, University of Manchester Medical School, Manchester

Clinical Background

Chronic/acute relapsing and remitting low back pain +/- sciatica (LBPS) is a major problem for society

- Will affect 40% of the population
- Point prevalence of 4-6%
- Impacts on
  - Society – Healthcare, Social services, Industry - £10 billion/annum
  - Individuals and families
- At least 60% discogenic

Role of the Intervertebral Disc
• Intervertebral disc (IVD) has 2 major components:
  o Inner nucleus pulposus (NP) – Hydrogel consisting mainly of aggrecan. Highly hydrophilic; generates a swelling pressure sufficient to push apart adjacent vertebrae even in the upright posture
  o Outer annulus fibrosus (AF) - Dense Collagen bundles, bind the vertebrae together and prevent excessive distraction

• Together the AF and NP allow movement between vertebrae and act as a spacer to maintain optimum mechanical function of the spinal elements around the IVD (motion segment)

• Four causes of discogenic back pain
  1. Loss of disc height and altered mechanics leading to microtrauma
  2. Ingrowth of nociceptive nerves into the usually avascular and aneural IVD
  3. Local synthesis of TNFα leading to excitation of nerve root
  4. Ischaemia

1. Loss of disc height

Due to:
• Decreased production of aggrecan
• Production of abnormal aggrecan
• Increased aggrecanase production

Leads to: decreased hydrogel effect; alterations in the biomechanics of the motion segment; spinal instability around the motion segment; microtrauma to insertions of AF into vertebra (traumatic enthesopathy); trauma to endplate; altered anatomy of the intervertebral root canal (leading to sciatic symptoms); facet joint disease

2. Nerve ingrowth

• Nerves grow into the normally aneural IVD
• Nerves are nociceptive – structure, Sub P
• Associated with angiogenesis
  o Endothelial cells secrete neurotrophins
  o Nerves responsive to neurotrophins – express high affinity receptors
• Altered matrix biology of the IVD
  o Changes in aggrecan promote (fail to inhibit) nerve ingrowth
• Altered cell biology of the IVD
  o IVD cells from degenerate discs promote nerve growth

3. Local production of TNF

• IVD degeneration is a cytokine mediated disorder (IL-1-driven)
• TNF also produced but particularly localised to protruding disc tissue
• Disc cells do not carry TNF receptors
• TNF said to exert a direct effect on nerve root (? DRG) via diffusion from disc tissue

4. Ischaemia

• Protruding disc tissue
  i. Compresses venous plexus
  ii. Leads to poor venous return and thrombosis
  iii. And ischaemic fibrosis of nerve root and loss of neural tissue

Potential strategies for research into new therapies
• Restore disc height – This will require a tissue engineering/regenerative medicine solution
• Influence nerve ingrowth – biological delivery (IDET)
• Inhibit TNF – local or systemic delivery of anti-TNF, prevent production of TNF
PAIN AND ARTHRITIS – DISCUSSION

1. One of the key tasks is better phenotypic characterisation of the different pains reported:
   a. need to separate, for instance, tenderness from pressure pain, movement-related pain and spontaneous pain
   b. It is unknown for example whether osteoarthritis or even joint pain is a separate entity
2. There is a role for genetics in, for example:
   a. comparing MRI abnormal subjects with and without pain
   b. a comparison of disease vs. no disease does not allow comment on genetic aspects of pain per se
3. Need to explain any mechanism of arthritis pain by disturbance of neurophysiologic processes
4. Demonstration of pathology may be most effectively done by imaging as opposed to conventional pathological means
5. One key unknown is the relation of central to peripheral drive in perpetuating joint pain
6. One interesting group to study are those who have had a joint replacement but still continue to complain of pain

SESSION II: IMAGING AND PAIN

GENERAL PRINCIPLES

Dr Karolina Wartolowska, FMRIB Centre, Oxford University

1. Joint pain
   • Musculoskeletal disorders are the most frequent cause of disability in developed world
   • Joint pain as the main reason of disability and impaired quality of life
   • There is no satisfactory treatment (limited effectiveness & side effects)
   • Enormous need for
     i. a better understanding what causes joint pain
     ii. an objective measure of pain
2. Why use fMRI to image pain?
   • Indirect measure of neuronal activity by measuring oxygen uptake which leads to changes in blood flow
   • Good spatial resolution and temporal precision
   • Non-invasive, no radioactivity
   • Can be used for repeated imaging or in longitudinal studies
   • Studies of increasing temperature leads to increase activity in anterior cingulated
   • Studies also showed regions that respond to analgesia, drug concentration effect
3. Areas of understanding neuro-anatomy of pain pathways
   • There are several brain regions that reproducibly activate in response to painful stimuli
   • Not a single structure responsible for generation of pain.
4. Pain is a complex experience that depends upon several factors:
   • Genetics
     o COMT polymorphisms have different responses
   • Cognition
     o Attention to pain leads to greater activity than distracted patients
     o Works also for anticipated pain and depends on how much they anticipated pain
   • Context and mood
Mechanisms of pain in arthritis

- Anxiety affects pain rating
- These are mediated in different parts of the brain
- Separate regions code for anxiety and severity
- Neuronal damage nociceptive
  - Will get amplified by physiological and psychological factors
- There are differences in the way arthritic and experimental pain are processed

5. Methodological approaches to imaging of clinical pain
- Imaging and differences between clinical and experimental pain.
- Imaging and influence of depression on clinical pain processing.
- Imaging and early effect of treatment
- Imaging of pathological phenomena such as allodynia

6. Summary
- The functional neuroimaging methods show reproducible brain activation in response to nociceptive stimuli
- Correlating the activation with what subject describes allows us to target components of pain experience such as anxiety or attention etc to be targeted
- Neuroimaging is useful for assessing mechanisms contributing to pain perception and thereby dissecting relevant components of the patient’s pain experience for more effective targeting of treatments

IMAGING PAIN - DISCUSSION

1. There is no doubt that imaging, especially fMRI is a useful tool in understanding pain physiology

2. The role of imaging in identifying causes is different from that in monitoring say treatment response, which is seldom investigated

3. It is not clear if imaging abnormalities should be considered as a biomarker of pain, a surrogate for pain or actually giving mechanistic insights

4. There are a number of detailed areas that need to be addressed in imaging studies including:
   a. different pain types (neuropathic/inflammatory etc)
   b. acute vs. chronic pain
   c. pain severity and associated symptoms such as fatigue
   d. differences between tenderness and pain

5. There are differences in real pain from imagined pain that need to be explored

6. It is not clear how far fMRI investigates the response to pain for example by invoking fear

7. Potentially the greatest benefit from imaging is from drug studies aiming to identify small effects and hence acting as a screen for new agents

8. In general therefore there is a strong need for longitudinal studies particularly of drug response

9. Imaging the periphery is well developed but it is not clear if studies are detecting inflammation or pain

10. Imaging the spinal cord is more complex due to CSF flow and other physiological responses

11. There is a need for more studies linking electrophysiology with imaging
**SESSION III: PHYSIOLOGY**

**CENTRAL PROCESSING**

*Anthony Jones, Professor of Neuro-Rheumatology, Human Pain Research Group, University of Manchester*

**Summary:**

Functional brain imaging techniques have facilitated the identification of the components of the human pain matrix (HPM) in the human brain and its main division of function. The relevance of this matrix to all types of experimental and clinical pain is now well established. The whole of the HPM has been shown to be as sensitive to ‘top-down’ and ‘bottom-up’ influences. The use of different types of functional brain imaging techniques has allowed us to begin to construct a dynamic model of human pain perception.

Whereas, only a small number of brain structures are influenced by the location of pain, the psychological context of pain is the most dominant influence on the pattern of nociceptive processing in the brain. PET (Positron Emission Tomography) and clinical pharmacological studies have established the role of endogenous opioid peptides and serotonin (5HT) in the modulation of nociceptive processing in the brain. Candidate mechanisms that may contribute to chronic pain states such as fibromyalgia and post-stroke pain have been identified. The combined use of sensitive physiological markers and psychological assessments will allow us to move towards defining common physiological phenotypes within the range of musculoskeletal conditions. This will facilitate the targeting of new pain mechanisms-based therapies. It will also lead to improved clinical trial design.

**Introduction:**

Pain is defined as; “a sensory and emotional response to actual or potential tissues damage”. Implicit in this definition is the very variable relationship between tissue damage and pain. This introduces the concept of the pain system as being as much a virtual reality system as other sensory systems. The actual experience of pain is the result of an integration of prior information (such as previous experience or warning about the pain) and current information (such that derived from an actual or apparently noxious stimulus). Functional brain imaging allows us to understand how these components are integrated. The effects of learning, attention, anticipation and mood on these processes are likely to be common to all types of pain but may vary substantially between individuals.

There is a very variable relationship between joint damage and pain in arthritis. Contributions from nociceptive (driven by tissue damage), psychogenic (e.g. chronic widespread pain-CWP) and neuropathic components (e.g. sciatica) will change over time. The strict attribution of pain to disease states is therefore quite tenuous in patients with arthritis. The temporal components of the pain may also be highly variable with combinations of recurrent acute and chronic persistent pain.

**Core Questions**

- What are the central mechanisms that explain the variable relationship between pain, disability and pathology?
- If such central mechanisms can be identified, can they allow us to develop new pain therapies?

**Functional brain imaging and related techniques: What questions have been answered?**

- The cerebral components of the human pain matrix (HPM) have been identified
• The main division of function within the pain matrix has been established: the lateral pain system processes mainly pain localisation, whereas the medial pain system processes mainly emotional affective and possibly motivational components of pain. The whole matrix is probably involved in intensity-coding.

• All types of experimental and clinical pain, including pain in patients with arthritis, are processed within the same matrix

• The HPM is as much modulated by ‘top-down’ (e.g. cognitive and affective components) as by ‘bottom-up’ influences (e.g. intensity of nociceptive input)

• Different patterns of response to experimental pain have been documented in patients with different types of chronic pain. Increased cortical responses within the anterior cingulate cortex have been observed in patients with somatoform pain disorders, whereas reduced cortical responses have been measured in patients with inflammatory arthritis and acute post-surgical pain. These differences are thought to be due to different attentional resources being devoted to pain processing in these groups.

• Confirmation of the latter hypothesis comes from PET and EEG studies where comparisons have been made between patients and normal controls which have shown clear differences in attentional response to pain. Patients with CWP are unable to switch their attention away from the unpleasantness of pain. EEG studies measuring anticipation and pain-evoked responses provide insight into the dynamics of these differences: Whereas normal controls use all the prior information (cues about the intensity of the stimulus) to elaborate their pain experience, patients with CWP are unable to do this.

• These and other findings suggest that there is a failure of endogenous pain control mechanisms in patients with CWP. These are potentially amenable to established and improved cognitive interventions.

• In addition patients with peripheral neuropathic pain and fibromyalgic pain can be differentiated on the basis of combined use of quantitative sensory testing and pain-evoked potentials

• The imaging of changes in occupation of opioid receptors in the brain has provided a way of indirectly measuring the activity of the endogenous opioid (EO) activity. It has been shown that the EO system is activated during both arthritis pain and neuropathic pain. The relative failure of this and related endogenous pain control systems represents an important translational target. New compounds are being developed to enhance EO activity specifically in the brain.

What are the strengths and limitations of current approaches to answering these questions?

• Functional brain imaging has provided candidate mechanisms for normal and abnormal pain perception that would not have been possible using animal models

• The combined use of physiological (e.g. EEG) and psychological measurements provides a potentially powerful and cost-effective way of defining clinical pain phenotypes, targeting new therapies and improving clinical trial design

• EEG and 18FDG PET provide methods of directly recording neuronal activity and are therefore the most robust ways of assessing analgesic effects on neuronal activity. In addition PET provides a way of establishing whether a potentially centrally acting analgesics penetrate the blood-brain barrier at an early stage in its development. Functional brain and spinal cord imaging also provide techniques with the capacity to measure neuro-inflammatory components of pain.

Barriers

• Techniques to measure spinal cord responses to pain in man are quite limited but methodologies are being developed to address this

• There is a knowledge gap as to how animal models of pain relate to different human pain phenotypes

• The main barriers to progress are the absence of nationally coordinated collaboration and funding between industrial and academic centres of excellence to resolve these issues
Suggested strategy for the future

The use of these techniques allows a mechanisms-driven approach to developing new therapies for pain. As other approaches have so far failed, it may be time for a paradigm shift.

PERIPHERAL PROCESSING

Stephen B McMahon, King’s College London and the London Pain Consortium

The last decade has seen considerable increases in our knowledge of peripheral pain mechanisms. As summarised in Figure 1, we now have detailed knowledge of many of the molecular identities that contribute to the transduction of sensory stimuli by nociceptors innervating the peripheral tissues of the body. We also have begun to understand the role of multiple ion channels, some unique to nociceptors, in regulating the excitability of these neurones. The central terminals of nociceptive afferents are also subject to physiological controls that regulate neurotransmitter release and again there has been considerable increased knowledge of what is released and how this is modulated, for instance in chronic pain states.

However, it is less clear if this newly discovered information applies specifically to joint pain. And this is important because it will determine whether any novel analgesic developed will be effective in treating different types of joint pain. On the other hand, if there are mechanisms that are specific to joint nociceptors, that too would be of therapeutic importance, potentially allowing the development of treatments specific for joint conditions. Techniques exist for resolving this issue by combining experimental studies in man and animals. Figure 2 summarises some of the key outstanding questions and the approaches that could be adopted to answer them.
Figure 2 Summary of key questions relating to peripheral mechanism of joint pain. The text in white gives some of the technologically feasible way of addressing these questions.

NEUROENDOCRINE AND GENETIC ASPECTS

John McBeth, Pain Research group, arc Epidemiology Unit, University of Manchester

Role for Neuroendocrine Input

Chronic musculoskeletal pain that is widespread throughout the body (CWP) is reported by approximately 10% of the general population. Symptom onset is strongly predicted by physical and psychological stressors. The biochemical mechanisms responsible for mediating and integrating the stress response associated with chronic pain in determining outcome are unclear. One potential mechanism of action is through the HPA stress response system.

When exposed to a stressor the key determinant to a successful adaptive response is both activation of the HPA axis and then shutting off this response after the stressor has passed. On activation, increased levels of corticosteroids, primarily cortisol, lead to physiologic and behavioural responses being initiated ultimately resulting in allostasis and adaptive mechanisms. Allostatic load refers to the physiological costs of chronic exposure to, among others, the neuroendocrine stress response and alterations in HPA axis function are considered to be an indicator of increased allostatic load. We conducted the first community-based studies to examine the relationship between CWP and the HPA axis and demonstrated that (1) CWP was associated with altered HPA axis function and (2) that among individuals who were free of CWP but at future risk, alterations in HPA axis function were associated with an increased risk of symptom onset. Specifically, subjects with higher evening saliva cortisol levels indicating a blunting of the diurnal rhythm, and those with higher post-dexamethasone serum cortisol levels indicating a failure to suppress the HPA axis, were at increased risk. The relationship of a hyper-responsive axis was independent of the effect of coexistent depressive symptoms and other psychosocial factors or sleep disturbance that may impact on the function of the HPA axis.

These findings are supported by previous reports of HPA axis dysfunction among clinic patients with widespread pain disorders. These patients have been shown to display a number of abnormalities of HPA function including a failure to suppress the axis after administration of dexamethasone, and a loss of the circadian fluctuation of glucocorticoid levels with elevated levels during the circadian nadir. Compared to sedentary and pain free controls patients with CWP display dysfunction of the HPA axis marked by hyper-reactive release of adrenocorticotropic hormone (ACTH) release in response to a challenge with corticotropin-releasing hormone (CRH) while patients with less widespread pain (non-inflammatory low back pain) displayed similar dysfunction but less marked when compared to the widespread pain group. Conclusions from these studies support the concept of disturbed HPA axis function in subjects...
Mechanisms of pain in arthritis

with chronic pain, and specifically with CWP. Disturbances in other stress-responsive endocrine systems including the growth hormone axis and the bioavailability of neurotransmitters including serotonin and substance P have been reported.

Interpretation of these findings is difficult since the majority of studies are cross-sectional and it is difficult to disentangle the temporal relationship between chronic pain and stress-system alterations. More importantly studies have tended to focus on single systems in isolation, uninformed of the complex interactions within and between systems.

Genetic Influences on Pain

Evidence from family and twin studies indicates that there is also a genetic component to chronic widespread pain syndromes that may confer a susceptibility to developing chronic pain in the presence of stress. Genetic association studies have focussed on the serotoninergic and catecholaminergic systems, and have also suggested a role of inflammatory mediators. No definitive pain susceptibility genes have yet been identified but the field is in its relative infancy compared to many complex diseases. The existing studies are subject to many study design issues. Careful consideration needs to be given to these when designing future studies into the genetic susceptibility of CWP, to ensure the robustness of findings.

The number of candidate genes implicated in pain is extensive due to the complex neurophysiology of pain and the long list of candidates proposed by animal studies. Current limitations in this field include inadequate study power due to limited sample size, limited adjustment for confounders, genetic variation within genes of interest insufficiently represented, and few attempts to replicate significant findings. Future genetic association studies of CWP should have adequate sample size for sufficient power to detect associations. Candidate gene selection should be based on strong biological rationale with supporting evidence from experimental and genetic studies and Tag SNP approaches should be used to capture the variation within the genes of interest based on linkage disequilibrium. Appropriate information on pain status and potential environmental and psychological confounders is also required to allow adjustment for confounders where appropriate. Finally, significant associations must be replicated in an independent data set.

Future research should also include genome-wide association studies, genomics, and studies of proteomic/metabolomics profiles. These approaches would provide powerful tools to elucidate key genes that are cost-effective compared to candidate gene approach and are likely to identify Important pain genes may be currently of unknown function that have not been identified by candidate gene studies.

PHYSIOLOGY - DISCUSSION

Physiology of Human Pain

1. It is unclear if pain processing in musculoskeletal disease is different from other chronic painful conditions, almost certainly they are different from say chronic dental pain
2. Central sensitization from afferents in skin may be different from musculoskeletal elements and this could explain different responses to drugs
3. It is essential that the adaptive pain phenotype is more robustly characterised though it is not clear whether this can be done by simple clinical means or if it requires sophisticated imaging
4. Imaging may help in distinguishing neuropathic, psychogenic and inflammatory pain
5. It is a target for research to understand if the descending pathways (from brainstem to spinal cord), either inhibitory or facilitatory are affected in chronic pain states. This could be a useful target for novel therapeutics though it is not clear how best to investigate these
6. There are likely to be genetic and ageing influences on the maladaptive pain response and again these are areas ripe for investigation. Micro-arrays may be a useful tool to explore in relation to pain
7. The role of surgery in leading to a neuroinflammatory response and hence perpetuation of pain should not be ignored
8. The drug pregabalin is an interesting compound as it appears to have effects at several levels which make it a useful investigatory tool.

SESSION IV: PSYCHOLOGY

PSYCHOLOGICAL ASPECTS

Chris Eccleston, University of Bath

A primer in psychology

Psychology as an academic subject was borne from physiology and philosophy. It has been influenced in its very short history by political developments in social science, methodological advancements in biological science, and fashionable attempts to make itself an applied science, offering opinions and expertise in subjects that range from marketing and business to individual personal change through psychotherapy. As a science it

a. Occupies territory not occupied by any other science; that is, the explanation, prediction and control of behaviour
b. Its theories draw on a wide range of other sciences, so such explanations can sometimes be based in the behaviour of molecules, and other times based in the behaviour of populations
c. It employs both deductive and inductive methods of inquiry. To the non-psychologist it can sometimes appear to be free-floating, at its worse it operates only to state the obvious, at its best it displays astonishing perspicacity, providing explanations that enable people to act.

Applied to pain what this means is that it is probably unhelpful to think that there is only one psychology of pain. There are at least three psychologies that are relevant here:

- “Cognitive” because it relates to private mental events, experiences of thought or perception
- “Social” because it relates to influences on behaviour that arise from our evolutionary imperative to behave collectively
- Clinical, because it relates to specific attempt to intervene with individuals or groups for a desired health related outcome

Cognition and brain science: The threat of pain

Pain needs to be understood as a biologically significant threat. It functions to alarm an organism of real or potential current or imminent danger. From this point of view, because pain functions as a threat, we should expect:

- Anxiety system involvement in its perception
- Motor system involvement because of the need to respond to threat
- Response to dominate over other competing demands

There is a strong and developing cognitive science of chronic pain, bolstered recently by developments in imaging physics, which has taught us the following:

- Pain involves multiple brain systems, with distributed involvement
- Pain is an affective-motivational event
- Pain requires attentional system involvement
- Pain is the perceptual product of lower order multiple perceptual systems
- Pain experienced chronically will chronically effect related systems (memory and attention, motor behaviour, self systems)
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- Belief systems are a very late stage occurrence in the perceptual process, dealing largely with the consequences of the interruption

Social Pain: Sharing and social sharing

People’s beliefs and expectations about pain are socially generated, mediated and communicated. It is helpful to understand pain as both a private mental event, and as a social event. People construct theories about their pain that drive their behaviour (e.g., “my knees are worn down”, “I have a disease that is eating away at me”, “it runs our family”). Such beliefs drive behaviour, and behaviour supports or reinforces the beliefs. Similarly pain communicates distress and danger to others, thereby promoting pain related behaviour in others, e.g., in offering or denying support. There have been many studies on the social psychology of pain and how people cope which have focussed on:

- Beliefs about disease, pain, and treatment
- Coping (as behaviour brought in response to threat)
- Social support (or lack of it)
- Characteristics of caregivers
- Individual differences in patient response (personality):
  - Anxiety (fear processes in particular)
  - Depression
  - Strength of beliefs (engagement, disengagement, acceptance)
  - Parental/Spousal influences

Clinical psychology: What can we do about it?

Any explanation, however elegant and engaging, is sterile without action potential. The evidence for psychological interventions in chronic pain in general (with a large number of studies in arthritis pain) is excellent. The psychological management of pain revolves around behaviour change and maintenance (either individually, dyadic, organizationally). Critical behaviours of focus are (treatment beliefs, return to work/school, negative self-appraisal). Largely the evidence base for successes and developments in this area comes from:

- Cochrane Reviews in Cognitive Behaviour Therapy for Adults with Chronic pain
- Cochrane Reviews in Psychological treatments for adolescents with Chronic pain
- Treatment developments in acceptance based methods
- Early workplace and school based interventions for prevention, and relapse prevention
- The use of third party agents (spouses, teachers, volunteers) in the promotion of self-management
- Comprehensive assessment methods, and classification systems to identify clusters of patients

What don’t we know?

Despite the promising advances in the psychology of chronic pain there remain some important unanswered questions/areas of research:

1. **Pre-conscious pain**
   Involvement of pre-conscious perceptual organization of pain, threat and flight mechanisms. Much of what matters in pain processing probably occurs pre-awareness, and understanding the sensory-perceptual organization of the sensory processing, including implicit awareness, attentional blindness, and sensory integration processes. Much of this work is aided by advances in neuroimaging, but will not be driven by imaging methods but by developing theory and experimental method.
2. **Novel psychological targets of pharmacological treatments**
   Much of the development in analgesics has been based on attenuating the sensory aspects of pain. Psychological theory suggests that the most aversive and disruptive aspects of pain is its ability to interrupt current attentional engagement. Drug development based on reducing its interruptive characteristics is in its infancy. It is possible to objectively measure the impact of pain on performance, and therefore the impact of analgesics on returning performance.

3. **Coping with “coping”**
   Four decades of coping research has failed to provide a unified and helpful theory of which treatments can be targeted for which outcomes in pain and arthritis. What is needed for each arthritis pain coupling is a specific psychological theory (prediction and control of behaviour) that leads to specific treatment recommendations (compare OA to AS for example). What is needed is a research investment that puts the patient first. For each presentation we should be able to map a model of why people behave as they do, right through to which specific treatment should be applied.

4. **Treatment non-compliance**
   There are excellent pharmacological and non-pharmacological treatments available for pain and arthritis but they are typically not prescribed or are not adhered to. Understanding failure to commission, failure to prescribe, and failure to adhere, is one of the major untapped sources of potential treatment success. This applies to common analgesic therapies, exercise and CBT.

5. **Chronic pain as a developmental disorder**
   The psychological literature is dominated by cross sectional comparisons with clinical samples. We know very little about natural adaptation in a chronic disease. Sorely needed is a model of the development of adjustment to pain and disease. This should be focussed on different life stages. There are key questions concerning early pain experience and neuro-development, adolescent social development, understanding adjustment in old age. Specific developmental models that focus on key adjustment phases, but combine neuro-developmental, and social developmental theory will be a major advance in pain science.

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**PSYCHOLOGICAL ASPECTS - DISCUSSION**

1. There is a need for more research into attempting to capture the private experience of pain and this will require better methods of measurement including assessment of fatigue

2. It is not known whether psychological influences only drive top down aspects of pain processing

3. Need to take account of beliefs as well as mood and this includes beliefs of health care professionals in treating pain

4. There are adverse effects of psychological interventions. Drop outs from therapy are a marker but we do not know what the long term consequences are

5. CBT is a valuable modality and could be delivered by computer
Introduction

Despite decades of intensive research, the research and development community have failed to succeed in bringing new pharmacotherapies to market for the treatment of pain associated with the arthritides (often collectively but inappropriately described under the banner of “inflammatory pain”). The outcomes of these efforts are a stark illustration of the immense challenge facing researchers, both from a basic scientific point of view, but also more recently from a regulatory perspective, where demand is increasing for placebo-like safety and side effect profiles.

In determining reasons for this failure, and steps which need to be taken to ensure success in the future, consideration must also be given to the overall requirements that novel pharmacotherapy must meet, and in this regard, the profile of the currently available therapies is the determining factor. The non-steroidal anti-inflammatory (NSAIDs and COX-2 inhibitors) class of therapies are effective in many acute and chronic pain settings, and form the mainstay of current therapy to address arthritic pain. Factors leading to escalation from “weaker” (e.g. paracetamol) to “stronger” (e.g. opioid-based therapies) are well understood, as is the use of routine polypharmacy to treat pain. In the majority of cases, patients obtain adequate (but often incomplete) relief from their pain, side effects are manageable, and chronic use is acceptable. The challenge of improving on these therapies should not be underestimated.

A number of recent findings should inform future research directions. However, one major caveat should be considered: in most cases, clinical studies of novel pharmacotherapies have not truly tested whether a new mechanism has the capability to produce meaningful pain relief. Of the 15 clinical studies across industry that this author is aware of, in greater than 90% of these studies the conclusion was that the target mechanism was not adequately tested.

One or more of the following was the most likely reason for failure to observe efficacy:

- inadequate systemic exposure
- inadequate central exposure
- study insufficiently powered
- failed positive control
- study inconclusive
- side-effect/tolerability profile unacceptable to escalate to sufficient dose
- violation of entry criteria.

This failure is the single most important reason for failure to provide novel pharmacotherapies; new target mechanisms are not being tested because either the molecules designed to test them, or the clinical study parameters (e.g. dose, safety margins etc), are inadequate.

Future research: findings and constraints

Taking into account the above, there are still many lessons to inform the direction of future research.

1. Examination of the mechanism of action of currently successful therapies reveals that in most cases, either site-site synergy, or interaction with the target at multiple levels on the pain pathway is prevalent. Thus, opioid agonists act at multiple sites within the brain, at the level of the spinal cord, and likely directly in the periphery at the level of sensory afferents. Similarly, there is evidence that COX inhibitors also act at
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multiple sites peripherally and centrally, and recent evidence shows upregulation of COX-2 in the cord following injury.1 Tramadol® provides a good example of polypharmacology in a single molecule. Taken together, these data indicate that intervention in the pain pathway at a single entry point may be less successful in treating pain.

2. Imaging and psychophysical studies have demonstrated that pain must be viewed as an experience in humans. Supraspinal processing is able to modulate this experience to increase or decrease the relative unpleasantness of sensation, and this also must be taken into account when considering future research. As the study of central perception and processing of pain is still in relative infancy, research here is likely to yield novel targets which have not been explored at all for pain.

3. Recent research now highlights the importance of understanding the interplay between the neuronal and immune systems, particularly with respect to neuro-glial signalling. Previously, pain was envisaged as a purely neuronal process, but there is now a wealth of evidence to support the notion that microglial and astrocyte activation is pivotal in the initiation and maintenance of pain (see 2). Clinical studies to test these hypotheses in humans are already underway, but further study is required to fully understand the dynamic and temporal relationship between glia and neurones in pain.

4. Finally, identification of new targets from humans, rather than animals, is essential. While this may seem like an obvious statement, most new targets are still conceived following identification of the presence of the target, or effects of modulation of this target, in animals or lower organisms. Recent data highlight the importance and power of using human genetic analyses to identify new targets 4, 5, and in this case the targets are de-facto “validated”. Large scale genetic studies of the association between SNPs and pain susceptibility are essential, and this remains a key unmet need at present.

Summary

Identification of targets whose modulation can be shown to affect pain processing in animals is straightforward; there are currently tens of such targets under active investigation. The challenge, though, is validating these targets to gain confidence that they will indeed modulate pain in humans, and then designing molecules and adequate testing paradigms in human to unequivocally test their efficacy. Significant progress is being made in these regards, but there remains an urgent need to revise target identification strategies towards using humans as the identification and validation organism (e.g. using genetic association studies) and revising clinical study strategies such that new targets can be genuinely tested. A combination of these revisions, plus intense mining of new areas of biology which include neuro-glial interactions, and modulation of supraspinal processing in humans, looks likely to reveal new targets with increased probability of success in demonstrating clinical efficacy in chronic pain associated with the arthritides.

References

1. The key challenge is not the identification of new targets but developing molecules that work

2. Of 100 targets identified typically only 2 compounds will enter Phase 2 studies

3. Main reasons for lack of efficacy include:
   a. insufficiently high concentration
   b. inability to cross blood brain barrier
   c. toxicity
   d. wrong patient population

4. Research probably best focussed on agents that have multiple sites of action as there is redundancy in processing pain

5. Compounds will differ in their effects on nociceptive vs. inflammatory vs. neuropathic pain

6. Perhaps the best strategy is to start in humans looking at proof of concept with biomarkers, then test in animals, then in human volunteers and then in carefully stratified clinical populations

7. Of potential novel targets the following offer exciting research opportunities:
   - Nociceptive pain processing
   - Altering the function of the cells in the rostral-ventro-medial medulla where there are ‘off’ and ‘on’ cells in relation to pain. Their physiological function is known but the molecular mechanisms underpinning these is less clear

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**ASSESSMENT OF PHYSIOLOGICAL AND OTHER THERAPIES**

*Bruce Kidd, Professor of Clinical Rheumatology, Barts & The London, School of Medicine & Dentistry, London*

**Introduction**

Numerous approaches based on modulation of physiological variables have been used to treat musculoskeletal disorders, including physical therapies, acupuncture, transcutaneous nerve stimulation and, more recently, correction of sensori-motor imbalance. Although most have been shown to be broadly effective in reducing pain, the mechanisms of action remain unclear in the majority of cases and clinical assessments in current use cannot predict the analgesic response in individual patients. Unresolved problems include the selection of patient populations that express defined mechanisms, and identification of reliable outcome measures to demonstrate the effect of treatment on specific pathways. The following paragraphs review some of these issues as well as proposing possible directions for future research. Although applicable to the use of physiological therapies the comments are also relevant to more general therapies.

**Recent developments – Pain mechanisms**

The characteristic feature of most chronic pains is that hitherto non-noxious stimuli, such as walking or standing, are perceived as painful. It is now clear that pain pathways, far from being static or hardwired, exhibit marked plasticity and that sensitization at peripheral, spinal and cortical levels accounts for many of the clinical features associated with
chronic pain. Consistent with this, the three chronic pain categories currently recognised, including neuropathic pain, neuroplastic or inflammatory pain and idiopathic pain, all exhibit features of an underlying sensitization state. The concept of a mechanism-based approach to therapy is based on the belief that characterisation of these features will permit the identification of the broad nociceptive processes operating in an individual.

A second approach to identification of particular pain phenotypes is based on the recognition that pain perception is dependent not simply on the intensity of neural activity ascending from the periphery to the brain but also on environmental and constitutional factors. Each individual has a unique experience of pain influenced by their life experience and genotypic profile. An individual’s stable psychological characteristics (trait) and the immediate psychological context in which pain is experienced (state) both influence perception of pain. Further, central nervous system processing associated with pain perception is closely integrated with hypothalamic-pituitary axis (HPA) and autonomic nervous system (ANS) activity. Variations in pain perception within populations may reflect genetic polymorphisms in all three systems, with current attention being focussed on serotonin transporter re-uptake protein (SERT-P), Alpha-2 receptor and catechol-O-methyltransferase (COMT) although a number of other candidate genes are under review. Current investigations are exploring whether stable sub-groups of psychological characteristics, grounded in differences in neurophysiological and neuro-endocrine reactivity, can serve to predict pain perception and responsiveness to therapy.

Assessment

The assessment of patients with chronic pain can utilize clinical bedside examination, quantitative sensory testing (QST), questionnaires, standard electrodiagnostic studies, laser evoked potentials (LEP), functional neuroimaging (fMRI and PET) and tissue biopsy. Whereas questionnaires are a formalised extension of the patient’s history, QST are a set of methods that extend the traditional examination of somato-sensory function.

A wide variety of quantitative testing procedures is available, each of which allows quantifying one particular aspect of sensory function. For the most part, QST has been used to study patients with neuropathic pain with far fewer studies having been performed in patients with musculoskeletal disorders. Primary and secondary hyperalgesia to both mechanical and thermal stimuli have been reported in a number of different musculoskeletal diseases. Functional studies using capsaicin have provided evidenced for enhanced central facilitation in subjects with rheumatoid arthritis whereas disturbances of descending inhibitory systems have been reported in osteoarthritic subjects that normalised after successful joint replacement surgery.

Objectives of future research

A key challenge is to characterise the somato-sensory phenotype of patients with musculoskeletal pain with the goal of testing the hypothesis that symptoms can be reliably linked to mechanisms across different diagnostics groups. The German Research Network on Neuropathic Pain (DFNS) has led the way in developing agreement with respect to testing protocols and establishing validated reference values as part of an on-going collaboration exploring neuropathic pain states. To date, no such collaboration exists nationally or internationally to explore pain arising from the somatic diseases.

Characterisation of the somato-sensory phenotype of patients with musculoskeletal disease will be facilitated by the development of a multi-centre national research network. Such a collaborative venture can work towards establishing validated assessment methodologies suitable for use in patients with arthritis. Large cohort studies of well characterised patients are needed to properly explore mechanistic subgroups, test new therapies and validate mechanism based algorithms. Such a collaborative venture will also serve to recruit and train young investigators and offers substantial promise for the future.

References

NOVEL THERAPEUTIC APPROACHES: PHYSIOLOGICAL - DISCUSSION

1. Need to consider the physiological consequences of pain when attended to or when ignored

2. Need to investigate the physiological (i.e. non-noxious) stimuli that make pain worse which could increase understanding of
   a. feedback systems and
   b. incongruent systems that lead to deterioration of pain

3. In all pain physiological systems there are important between-individual variations which should be explored

4. Physiological studies need to account for the powerful effects of mood

BEHAVIOURAL APPROACHES

Professor Gary MacFarlane, University of Aberdeen

Introduction

Behavioural therapies, together with exercise and physical therapies, are the non-pharmacological therapies that are most commonly used in the management of pain conditions in both primary and secondary care. Within behavioural therapies the most common types of therapy used have been:

- operant (positive reinforcement of healthy behaviours, time contingent and with spousal involvement)
- cognitive (identifying and altering patients cognitions regarding pain and disability)
- respondent (modifying physiological response systems).

Despite their popularity in primary care settings, however, the randomised controlled trials which have evaluated their effectiveness have generally produced disappointing results. In the following sections examples pertaining to low back pain will be used – since this is the most common pain condition presenting to general practice, there is the greatest evaluation of therapies, and the results are reflective of other common musculoskeletal pain syndromes.

Effectiveness of behavioural and physical therapies in back pain

The data

The UK BEAM study, a study of approximately 1300 patients consulting to general practice with an episode of low back pain, evaluated exercise classes and spinal manipulation and found that there was only at best a modest improvement, as assessed by the Roland and Morris disability scale (Roland and Morris, 1993), over 12 months for either the exercise, manipulation or both interventions over usual care (UK BEAM, 2004). A further UK trial compared, amongst approximately 300 patients referred to physiotherapy for low back pain, a usual course of physiotherapy with a single assessment advice session from the physiotherapist but over the course of twelve months found no significant difference in outcome (Frost et al, 2004) on the same scale. Hay et al (2005) compared a brief pain management programme with a traditional course of physiotherapy amongst approximately 400 persons consulting their general practitioner with low back pain in North-West England and found identical outcomes on the Roland and Morris disability scale 12 months later as well as levels of satisfaction with care amongst persons receiving both treatments. Jellema et al (2005a) in a cluster randomised controlled trial in the Netherlands focussed on general practitioners identifying and addressing psychosocial barriers to recovery (such as fear-avoidance, catastrophising and distress) amongst persons consulting with low back pain. General practices were allocated either to deliver usual care or to deliver a psychosocial-focussed care in a consultation which lasted 20 minutes rather than 10mins and where the general practitioners had received special training to deliver the intervention. However over the course of the year there was no difference in outcome on the Roland and Morris disability scale and moreover, the intervention failed to
result in any relative improvement in the hypothesised mediators of improved outcome (Jellema et al, 2005b). Finally, a recent trial amongst approximately 250 persons consulting their general practitioner with low back pain and who still reported pain and disability after three months, found that the outcome with written and taped advice and a physiotherapist led exercise class (but where the physiotherapist had received special training in cognitive behavioural therapy) was identical over the subsequent fifteen months (Johnson et al, 2007).

Why then have the results of behavioural and other non-pharmacological therapies in primary care been disappointing when the evidence base for their use is generally good. For example a recent Cochrane review concluded on the basis of 21 studies (7 of which were high quality) that “...combined respondent-cognitive therapies .....are more effective than waiting list control” for low back pain. It did however additionally conclude that there was “No significant difference between behavioural treatment and exercise therapy” (Ostelo et al, 2005).

Discussion

Firstly the interventions provided in primary care have generally used a “one-size-fits-all” approach i.e. the same intervention is applied to all persons in the trial (e.g. typically persons consulting to the general practitioner with low back pain). However it has been demonstrated that on the basis of a few simple measures (typically demographic, clinical, behavioural/emotional and/or psychosocial) (e.g. Thomas et al, 1999; Pincus et al, 2002) that population groups with a likelihood of a poor outcome ranging from around 5% to 75% can be distinguished. It seems an intuitive approach that usual care is particularly appropriate for persons predicted to have a poor outcome, while more intensive specialised care be reserved for those likely to have a poor outcome. Secondly persons who have an episode of low back pain will have different patterns of risk factors. Some may exhibit high levels of psychological distress, specific aspects of health behaviour (e.g. fear avoidance, catastrophising, passive coping strategies) while others may have principally physical risk factors (e.g. sports injury). While in current research studies the same package of care is likely to be offered to all persons with low back pain, it seems again a more intuitive approach to tailor the intervention to the risk factors present. For example, in a recent study of persons in an outpatient setting with fibromyalgia, patients were offered cognitive (CBT), operant behavioural therapy (OBT) or an attention placebo. Overall persons receiving the CBT and OBT improved more than those receiving the attention placebo. Patients responding to the CBT were those with affective distress and poorer coping styles while those responding to the OBT were those with greater illness behaviour, physical impairment, physician visits, solicitous spouse behaviour and catastrophising (Thieme et al, 2007). Further there is emerging evidence that another factor influencing response may be patient preference. In the previously-mentioned trial of physiotherapist led group exercise programmes for low back pain (where the physiotherapist had been trained in CBT) which showed no improvement in outcome against written and taped advice, participants were asked before randomisation what their preference was for treatment. Amongst those who expressed a preference for the active intervention those who received this intervention did better than those who did not. Similarly amongst those who expressed a preference for the advice arm of the trial, those who received this did better than those who received the active intervention (Johnson et al, 2007). This potential importance of patient preference has been supported by a recent individual patient meta-analysis of musculoskeletal trials which showed that a priori patient preference was associated with a significant effect on outcome (D-Torgerson, personal communication).

Finally, it may be argued that our expectations of improvement (whether it be function or pain) in recent clinical trials have been unrealistic. Delivering short interventions – many of which are focussed around one modality- to everyone consulting with low back pain, a condition for which we know the aetiology is multi-factorial does not seem likely to result in large improvements in most consulters. Perhaps we also have to re-assess what can reasonably be expected of such approaches and to evaluate what effect small improvements in outcome for individuals has at a population level.

References

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NOVEL THERAPEUTIC APPROACHES: PSYCHOLOGICAL – DISCUSSION

1. One of the key challenges is subgrouping pain using a simple bedside approach
2. One key research area is whether behavioural therapies make pain worse and if so why?
3. There is a need also to measure expectations and preferences before studying effects of a specific intervention
4. Outcomes from psychological interventions may be modest and it maybe necessary not to set goals that are too ambitious
5. In terms of CBT, need to think about ‘dose’ e.g. amount of hours and its effect
6. In all studies of psychological interventions there is a role for qualitative add on studies to inform understanding of mechanisms
7. Investigative questionnaires may act as an intervention, and this influence needs to be considered in evaluating therapeutic effects
APPENDIX 1: PROGRAMME

arc Research Strategy Workshop: Mechanisms of Pain in Arthritis

Chancellors’ Conference Centre, University of Manchester

November 29/30th 2007

Thursday 29th November:

12:30-13:00  Arrival and registration
13:00-14:00  Lunch
14:00-14.10  Introduction and goals of meeting  Alan Silman

Session I: Pain and Arthritis

14:10-14:30  Animal models of pain  Stuart Bevan
14:30-14:50  Discussion  Chair: Iain Chessell
14:50-15:10  Pain and arthritis: Rheumatoid Arthritis  Marzia Malcangio
15:10-15:30  Pain and arthritis: Osteoarthritis  Candy McCabe
15:30-15:50  Pain and arthritis: Disc disease  Tony Freemont

15:50-16:10  Coffee break
16:10-16:40  General discussion on Pain Mechanisms  Chair: Paul Dieppe

Session II: Imaging and Pain

16:40-17:10  Imaging and Pain: general principles  Karolina Wartolowska
17:10-17:40  Discussion  Chair: Praveen Anand

Special Session: arc Clinical Studies on Pain

17.40-18.00  arc Programme Discussion  Elaine Hay
19:30-20:00  Pre-dinner drinks
20:00  Dinner
**Friday 30th November:**

08:00-08:30 Breakfast

**Session III: Physiology**

08:30-09:00 Central processing: Overview  *Anthony Jones*
09:00-09:10 Q&A
09:10-09:40 Peripheral processing: Overview  *Stephen McMahon*
09:40-09:50 Q&A
09:50-10:10 Endocrine and genetic aspects: Overview  *John McBeth*
10:10-10:20 Q&A

10:20-10:40 **Coffee Break**

10:40-11:10 General discussion on physiology  *Chair: Mervyn Maze*

**Session IV: Psychology**

11:10-11:40 Psychological aspects: Overview  *Chris Eccleston*
11:40-12:10 General discussion on psychological aspects  *Chair: Stan Newman*

**Session V: Novel Therapies**

12:10-12:30 Pharmacological approaches: Overview  *Iain Chessell*
12:30-12:55 General discussion on Pharmacological approaches  *Chair: Susan Brain*

12:55-13:40 **Lunch**

13:40-14:00 Physiological approaches: Overview  *Bruce Kidd*
14:00-14:25 General discussion on Physiological approaches  *Chair: David Blake*
14:25-14:45 Behavioural approaches: Overview  *Gary Macfarlane*
14:45-15:10 General discussion on Behavioural approaches  *Chair: Elaine Hay*
15:10-15:15 Wrap up  *Alan Silman*