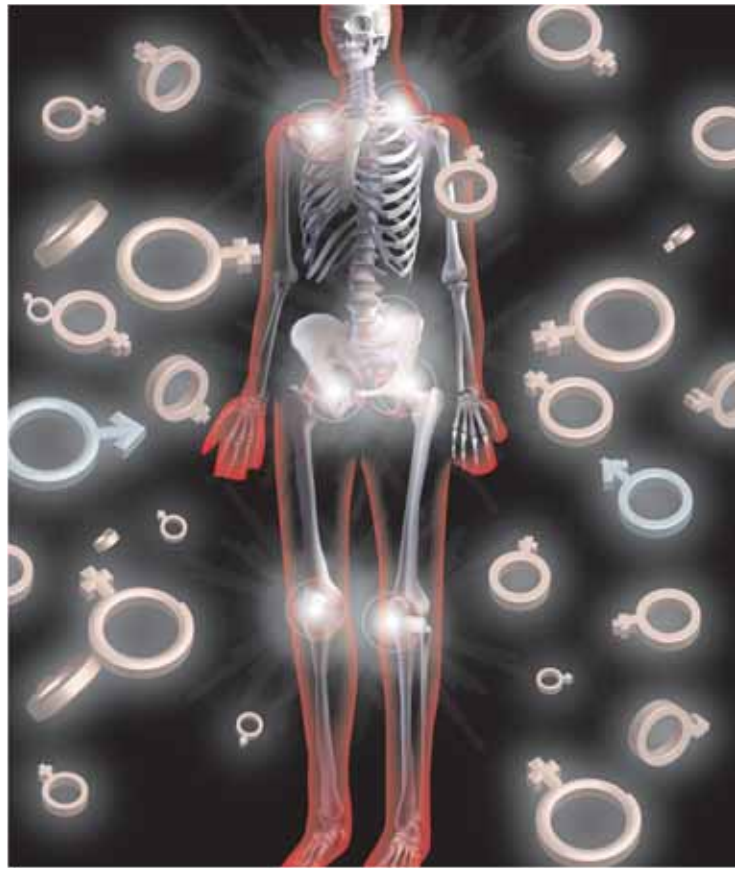
New evidence may explain why conditions such as fibromyalgia affect more women than men

It is widely accepted that chronic pain and fatigue conditions such as fibromyalgia are more common in women than in men. In fact, approximately nine out of ten reported cases of fibromyalgia occur in women. Furthermore, 94% of patients diagnosed with chronic fatigue syndrome report musculoskeletal pain and as many as 75% of patients diagnosed with muscle pain report fatigue. This shows that the two symptoms appear to occur concurrently and therefore may be linked to one another. Recent research led by Kathleen Sluka at the University of Iowa (IO, USA) has shown that there may indeed be a link between muscle pain and fatigue. In addition, researchers have also provided some evidence as to why women have a higher predisposition to these conditions than men.



In order to investigate the link between muscle fatigue and pain, and the higher rate of occurrence of these conditions in females, Sluka's team induced muscle fatigue, through exercise, in both male and female mice with or without the ASIC3 protein – an ion channel protein shown to have an involvement in musculoskeletal pain.

The mice underwent two exercise protocols: the first task involved three 1-h runs whereas the second task involved three 30-min runs. No difference in fatigue was observed in the second task. However, in the first task, male ASIC3$^{+/+}$ mice displayed less fatigue than male ASIC3$^{-/-}$ mice and female ASIC3$^{+/+}$ mice.

The researchers then investigated whether muscle fatigue is influenced by gender. Tests showed that female mice that were ovariectomized and given testosterone developed less muscle fatigue than female ASIC3$^{+/+}$ mice and showed greater similarity to male ASIC3$^{+/+}$ mice. Interestingly, ovariectomized female ASIC3$^{-/-}$ mice that were administered testosterone displayed muscle fatigue. This shows that the administration of testosterone was not able to increase muscle strength in ASIC3$^{-/-}$ mice. In addition, ASIC3$^{-/-}$ male mice showed significantly lower testosterone plasma levels than ASIC3$^{+/+}$ male mice and had testosterone levels similar to female ASIC3$^{+/+}$ mice.

Collectively, these results show that a combination of ASIC3 and testosterone is required to protect against muscle fatigue and gives a better indication of why chronic pain and fatigue predominate in women. "The differences in fatigue between males and females depends on both the presence of testosterone and the activation of ASIC3 channels, which suggests that they are interacting somehow to protect against fatigue", Sluka said. "These differences may help explain some of the underlying differences we see in chronic pain conditions that include fatigue with respect to the predominance of women over men."

This study also indicates that musculoskeletal pain and fatigue appear to be intertwined in that they may share a common mechanism or pathway. Studies such as this will help further the understanding of disorders such as fibromyalgia and will help researchers work towards potential therapies for such conditions. Sluka confirms that the long-term goal of her research team is to "come up with better treatments for chronic musculoskeletal pain". She adds, "[fatigue] leaves people unable to work or engage in social activities. If we could find a way to reduce fatigue, we could really improve quality of life for these patients".

Sources: www.sciencedaily.com/releases/2008/04/080407153037.htm; Burnes LA, Kolker SJ, Danielson JF *et al.*: Enhanced muscle fatigue occurs in male but not female ASIC3$^{-/-}$ mice. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 294(4), 1347–1355 (2008).

Priority Paper Alerts

Rituximab inhibits structural joint damage in rheumatoid arthritis patients with an inadequate response to tumor necrosis factor inhibitor therapies.

Keystone EC, Emery P, Peterfy CG *et al.*: *Ann. Rheum. Dis.* (2008) DOI:10.1136/ard.2007.085787 (Epub ahead of print).

Rheumatoid arthritis is an autoimmune disorder affecting approximately 350,000 people in the UK. Currently, one method of therapy against rheumatoid arthritis is the administration of TNF inhibitors. However, not all patients respond effectively to this treatment. Recent research has now found that rituximab can inhibit structural joint damage in patients who do not respond to anti-TNF-α therapy. In a Phase III study, patients were randomized to either rituximab or placebo. Radiographs were taken at baseline, week 24 and week 56, following randomization. It was found that treatment with rituximab caused a notable decrease in joint damage in comparison with placebo. This trial is the first study to demonstrate the effective use of rituximab in considerably inhibiting the progress of structural joint damage in patients suffering from rheumatoid arthritis.

Angiotensin-converting enzyme inhibition improves vascular function in rheumatoid arthritis.

Flammer AJ, Sudano I, Hermann F *et al.*: *Circulation* 117(17), 2262–2269 (2008).

Patients suffering from rheumatoid arthritis have an increased cardiovascular risk, since the inflammation that occurs during arthritis is linked to cardiovascular risk. In this study, researchers investigated whether the angiotensin-converting enzyme inhibitor ramipril can improve the vascular function of rheumatoid arthritis sufferers. The trial was a randomized, double-blind, crossover study involving 11 patients with rheumatoid arthritis. Patients were administered ramipril, in an uptitration design (from 2.5 to 10 mg), for 8 weeks followed by placebo, or vice versa, along with standard anti-inflammatory therapy. Flow-mediated dilation of the brachial artery was used to assess endothelial function. Markers of inflammation, oxidative stress and disease activity were also analyzed before and after treatment. It was found that following treatment with ramipril, endothelial function had increased. No change was observed with placebo. This significant improvement in vascular function suggests that angiotensin-converting enzyme inhibitors can be used in patients suffering from rheumatoid arthritis to prevent the risk of cardiovascular events.

Genome-wide search identifies genes linked to osteoporosis and fracture

Osteoporosis is an inherited disorder that results in a decrease in bone density. It affects approximately five out of 100 people in the UK, but has a higher incidence in women. In fact, osteoporosis is four-times more common in women than men, and mainly affects women after menopause.

'Identification of genes linked to osteoporosis not only gives researchers a better understanding of the disease and its mechanisms but could also lead to better diagnoses and improved treatment.'

Until now, only a few genes out of the 30,000 in the human genome have been found to have a link to osteoporosis. However, a collaborative effort from The Garvan Institute for Medical Research (Sydney, Australia) and deCode Genetics (Reykjavik, Iceland) has now identified a number of markers that are associated with bone mineral density and fragility fractures.

The study used genome-wide genotyping to analyze samples from 1500 women from Garvan's Dubbo Osteoporosis Epidemiology Study, in addition to more than 12,000 women from Iceland and Denmark.

"Genome-wide genotyping, a very demanding and labour-intensive procedure, measures genetic variations called 'Snips' (SNPs or single nucleotide polymorphisms), within each of our 30,000 genes", explained Tuan Nguyen from The Garvan Institute for Medical Research. "The collaborative study examined more than 300,000 such markers and found 12 that were linked to bone mineral density and 6 linked to fragility fractures. Some of these Snips are close to genes that are already known to be associated with osteoporosis."

Identification of genes linked to osteoporosis not only gives researchers a better understanding of the disease and its mechanisms but could also lead to better diagnoses and improved treatment.

Sources: Styrkarsdottir U, Halldorsson BV, Gretarsdottir S *et al.*: Multiple genetic loci for bone mineral density and fractures. *N. Engl. J. Med.* (2008) (Epub ahead of print); www.sciencedaily.com/releases/2008/04/080430091115.htm

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in the field of rheumatology.

If you have newsworthy information, please contact:

Grainne O'Keeffe, Commissioning Editor,
Future Rheumatology;
Future Medicine Ltd, Unitec House, 2 Albert Place, London N3 1QB, UK
Tel.: +44 (0)20 8371 6090; Fax: +44 (0)20 8343 2313
g.okeeffe@futuremedicine.com

Stem cell therapy may offer new hope for osteoarthritis sufferers

Osteoarthritis is the most common form of arthritis, affecting more than 2 million people in the UK. Osteoarthritis occurs when the cartilage in the joints gradually degrades over time, causing pain and swelling. A complete loss of cartilage will cause the bones to rub together, which can result in severe pain and permanent damage of the joint. Osteoarthritis can develop in any joint, but usually affects the hips, knees, hands and spine.

'Researchers ... have now identified cells in human cartilage that act like stem cells.'

Currently, one treatment for osteoarthritis patients involves transplanting healthy cartilage cells into the damaged area. However, the number of cartilage cells harvested from the patient is limited, making this treatment unsuitable.

Researchers at Cardiff University (Cardiff, UK), led by Charlie Archer, have now identified cells in human cartilage that act like stem cells. Although these cells can not differentiate into any type of cell, they do have the ability to differentiate into chondrocytes (cartilage cells) in large quantities. Therefore, were this technique proven to be successful, it would make effective transplantation a real possibility.

Although identification of these stem cells gives hope to arthritis sufferers, it is currently only being considered to treat those with cartilage damage. However, Archer and his team highlight the importance of this research: "This research has the potential to be significant if the findings in the laboratory can be translated to patients. It may be the key to slowing down the progression of the disease, reducing the need for joint replacements".

"This research may be the key to slowing down the progression of the disease, reducing the need for joint replacements."

Archer also commented, "We have embarked on the next stage which is to conduct an animal trial which is a necessary pre-requisite to a clinical trial which we hope to start next year if the results are positive".

Sources: www.sciencedaily.com/releases/2008/04/080411085922.htm; www.bupa.co.uk/health_information/html/health_news/180408_stem_cell_arthritis.html

Possible link between glutamate levels and pain in fibromyalgia

Fibromyalgia is a chronic rheumatic disorder that is characterized by widespread pain and fatigue in muscles and ligaments in all four quadrants of the body. Fibromyalgia mainly affects women and usually develops between the ages of 30 and 60 years; however, it is known to affect people of any age, including children and the elderly.

Recent research conducted by scientists at the Chronic Pain and Fatigue Research Center at the University of Michigan (MI, USA) has found that changes in glutamate levels may be associated with pain in fibromyalgia.

Previous studies had shown that a particular region of the brain, the insula, exhibits high levels of activity in patients suffering from fibromyalgia. Researchers at the University of Michigan hypothesized that this high activity might be related to high levels of the neurotransmitter glutamate. The involvement of glutamate in pain-processing pathways is well known, and this led the researchers to further investigate the role of glutamate in pain-associated fibromyalgia.

'...glutamate has an involvement in fibromyalgia and could be used as a potential biomarker of this disease.'

Researchers used functional MRI and proton magnetic resonance spectroscopy (H-MRS) to study changes in activity in the insulas of fibromyalgia patients. Acupuncture was used to alleviate pain symptoms in patients for a period of 4 weeks. H-MRS was performed before and after treatment. Following treatment, patients were reported to have reduced pain. Furthermore, this was correlated with decreased glutamate levels in the insula, where patients who exhibited greatly reduced pain showed a greater reduction in glutamate levels.

These data suggest that glutamate has an involvement in fibromyalgia and could be used as a potential biomarker of this disease. However, further work is required in order to better elucidate the role of glutamate in fibromyalgia. Were the results proven to be reproducible, the glutamate pathway could serve as a means of treating or alleviating the symptoms of fibromyalgia, thus allowing patients an improved quality of life.

Sources: www.sciencedaily.com/releases/2008/03/080310112658.htm;

Harris RE, Sundgren PC, Pang Y *et al.*: Dynamic levels of glutamate within the insula are associated with improvements in multiple pain domains in fibromyalgia. *Arthritis Rheum.* 58(3), 903–907 (2008).