Editorial

Building up the pressure on chronic pain

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Chronic pain remains one of the most frequent, and frustrating challenges of modern medicine. While recent decades have witnessed huge progress in combating such age-old foes as inflammatory joint disorders and even the fields of oncology and haematology are making progress head-over-heals, patients suffering from chronic pain, and particularly chronic widespread pain, with all its perplexing comorbidities, continue to be treated on a highly empirical and only partially successful basis. The reasons behind this reality are far from clear. To some extent one might speculate on the societal changes which have taken place over years in this aspect; what once would have been considered a condition calling for a stiff-upper-lip and stoic acceptance, now has gradually been recognised as a medically unmet problem with far-reaching effects on all aspects of human health and function. Notably, as chronic pain remains a condition with a clear female preponderance, it is tempting to speculate on how gender-bias may have reflected on resource-allocation and scientific focus into this area. Nonetheless, as Bob Dylan stated (so-many years ago) – the times they are a-changin. Currently, chronic pain, of which fibromyalgia remains a quintessential example, has at long last been recognised as a major healthcare issue to be dealt with, studied and taken seriously. Moreover, the huge economic impact of conditions such as fibromyalgia are coming to be acknowledged (1), an awareness which should lead to increased investment in understanding the science behind chronic pain and what we can do to intercept it. In this endeavour, fibromyalgia, a condition which has been berated and scorned by many, has proved to function as a most useful paradigm for studying and understanding the neurological underpinnings of chronic pain. Research conducted on fibromyalgia patients more than a decade ago (2) objectively illustrated for the first time how pain processing centers in the brains of fibromyalgia patients hyper-react to a peripheral pain stimulus, when compared with normal individuals, thus illustrating that pain hypersensitivity is a neurological reality, not a myth. Since these ground-breaking studies were performed, a great deal of additional progress has been made into understanding what might go wrong in the central nervous system of fibromyalgia patients, and how these derangements may be relevant for treatment. Thus, recent studies conducted on resting – state connectivity analysis, have demonstrated patterns of increased connectivity between the default mode network (DMN), and pain processing areas such as right anterior and right middle insula (3). Moreover, chronic pain intensity was associated with intrinsic brain connectivity. In another study, decreased connectivity could be demonstrated between pro-nociceptive and anti-nociceptive pain regions, and specific patterns could predict either the response to milnacipran, a noradrenaline – serotonin reuptake inhibitor or to placebo (4).

Additional exciting progress is being made through the implementation of other modalities as well. Magnetic resonance spectroscopy is a technique capable of measuring real – time levels of specific neurotransmitters. Using this method, Foerster *et al*. were able to demonstrate a decrease in the concentration of the inhibitory neurotransmitter GABA in the right anterior insula of fibromyalgia patients (5), thus shedding light on an additional possibility for both developing an objective biomarker and for identifying a treatment – target. These and other lines of evidence, which continually forward our appreciation of the complexity of the biol-

ogy of chronic pain within the CNS, as well as its interaction with the autonomic nervous system (6-8), make it ever – more tempting to search for novel ways in which one might be able to change intricate pain mechanisms through neuroplasticity. This concept is particularly appealing when one bears in mind that chronic pain is not "hard-wired" into our brains. Indeed, chronic pain in general, and fibromyalgia in particular, are not congenital; these conditions rather evolve over lifetime, often in response to various external influences such as trauma, stress or infection, thus emphasising the capacity of the CNS to morph and re-wire, even at a fully developed stage. Hence, the general concept of neuro-plasticity is almost inherent in the clinical evolution of chronic pain.

It is on this background that hyperbaric oxygen therapy (HBOT) has been suggested as a possible treatment for fibromyalgia. HBOT, which is the application of a combination of hyperbaric pressure and increased oxygen content, has previously been shown to have the capacity to induce neuroplasticity in injured brains even months to years after acute insult (9-12). In animal models, HBOT has been shown to have an anti-nociceptive effect which was mediated through the NO-dependent release of endogenous opiods (13) and could be inhibited by naltrexone, an opiod antagonist (14). Animal models have also demonstrated the efficacy of HBOT for inflammatory pain (15).

In humans, HBOT has been studied in a number of models of pain with encouraging results. As previously reviewed by Bennett *et al*., HBOT has shown efficacy in relieving acute migraine pain although it was not shown to prevent future attacks (16). HBOT has also been tested with some benefit in complex regional pain syndrome (CRPS) (17) and in trigeminal neuralgia (18).

To date, two randomised controlled trials have tested the efficacy of HBOT in fibromyalgia. In the first, 26 patients received fifteen 90- minute HBOT sessions at 2.4 ATA over 3 weeks, while 24 control patients breathed air at 1 ATA for 90 minutes (19). A significant decrease was observed in both the number of tender points as well as in the pain threshold in the HBOT group, compared to the sham treatment group.

In the second study, which was a prospective, randomised, controlled cross-over protocol, sixty female patients underwent 40 90-minute sessions of HBOT at 2 ATA. In this study HBOT treatment was associated with a significant improvement in pain thresholds as well as fatigue, distress and quality of life (20).

So how might hyperbaric oxygen be influencing the CNS, causing neuroplasticity and improving chronic pain? The answers to these interesting questions remain incompletely understood. Chronic pain has repeatedly been linked to the activation of immune – competent cells within the CNS such as microglia (21), leading to production of pro-inflammatory cytokines, chemokines and extracellular proteases, and at least in animal models HBOT has been shown to have positive effects on glia cell over-activation. Nonetheless, leaping to the conclusion that HBOT improves chronic pain through glia – deactivation is way beyond our current knowledge. Obviously what has to be done now, in addition to replicating previous results, is to further investigate the direct effects of HBOT on the available markers we have of deranged brain function in chronic pain – *e.g*. test how HBOT alters connectivity patterns in conditions such as fibromyalgia, how it changes levels of relevant neurotransmitters, and to what extent these effects correlate with clinical change.

Thus, while it is yet early to consider HBOT a standard part of treatment for fibromyalgia, the story of HBOT in chronic pain appears to have many chapters and sequels to anticipate. Ultimately, one would aspire to understand specifically what neuroplasticity means in the context of HBOT, and which targets are being affected in the CNS of fibromyalgia patients receiving this treatment. Issues such as safety and long-term outcome (including the need for maintenance treatment) also need to be clarified. Nonetheless, HBOT may eventually gain its due place in the armamentarium of physicians and patients struggling with chronic pain.

References

1. CHANDRAN A, SCHAEFER C, RYAN K, BAIK R, MCNETT M, ZLATEVA G: The comparative economic burden of mild, moderate, and severe fibromyalgia: results from a retrospective chart review and cross-sectional survey of working-age U.S. adults. *J Manag Care Pharm* 2012; 18: 415-26.
2. GRACELY RH, PETZKE F, WOLF JM, CLAUW DJ: Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum* 2002; 46: 1333-43.
3. NAPADOW V, LACOUNT L, PARK K, AS-SANIE S, CLAUW DJ, HARRIS RE: Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. *Arthritis Rheum* 2010; 62: 2545-55.
4. SCHMIDT-WILCKE T, ICHESCO E, HAMPSON JP *et al*.: Resting state connectivity correlates with drug and placebo response in fibromyalgia patients. *Neuroimage Clin* 2014; 6: 252-61.
5. FOERSTER BR, PETROU M, EDDEN RA *et al*.: Reduced insular γ-aminobutyric acid in fibromyalgia. *Arthritis Rheum* 2012; 64: 579-83.
6. ZAMUNER AR, BARBIC F, DIPAOLA F *et al*.: Relationship between sympathetic activity and pain intensity in fibromyalgia. *Clin Exp Rheumatol* 2015; 33 (Suppl. 88): S53-S57.
7. GRACELY RH, SCHWEINHARDT P: Key mechanisms mediating fibromyalgia. *Clin Exp Rheumatol* 2015; 33 (Suppl. 88): S3-S6.
8. GIACOMELLI C, SERNISSI F, SARZI-PUTTINI P, DI FRANCO M, ATZENI F, BAZZICHI L: Fibromyalgia: a critical digest of the recent literature. *Clin Exp Rheumatol* 2013; 31 (Suppl. 79): S153-S157.
9. EFRATI S, FISHLEV G, BECHOR Y *et al*.: Hyperbaric oxygen induces late neuroplasticity in post stroke patients - randomized, prospective trial. *PLoS One* 2013; 8: e53716.
10. HADANNY A, GOLAN H, FISHLEV G *et al*.: Hyperbaric oxygen can induce neuroplasticity and improve cognitive functions of patients suffering from anoxic brain damage. *Restor Neurol Neurosci* 2015; 33: 471-86.
11. BOUSSI-GROSS R, GOLAN H, VOLKOV O *et al*.: Improvement of memory impairments in poststroke patients by hyperbaric oxygen therapy. *Neuropsychology* 2015; 29: 610-21.
12. BOUSSI-GROSS R, GOLAN H, FISHLEV G *et al*.: Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury - randomized prospective trial. *PLoS One* 2013; 8: e79995.
13. CHUNG E, ZELINSKI LM, OHGAMI Y, SHIRACHI DY, QUOCK RM: Hyperbaric oxygen treatment induces a 2-phase antinociceptive response of unusually long duration in mice. *J Pain* 2010; 11: 847-53.
14. GIBBONS CR, LIU S, ZHANG Y *et al*.: Involvement of brain opioid receptors in the anti-allodynic effect of hyperbaric oxygen in rats with sciatic nerve crush-induced neuropathic pain. *Brain Res* 2013; 1537: 111-6.
15. WILSON HD, TOEPFER VE, SENAPATI AK, WILSON JR, FUCHS PN: Hyperbaric oxygen treatment is comparable to acetylsalicylic acid treatment in an animal model of arthritis.

J Pain 2007; 8: 924-30.
16. BENNETT MH, FRENCH C, SCHNABEL A, WASIAK J, KRANKE P: Normobaric and hyperbaric oxygen therapy for migraine and cluster headache. *Cochrane Database Syst Rev* 2008; 3: CD005219.
17. KIRALP MZ, YILDIZ S, VURAL D, KESKIN I, AY H, DURSUN H: Effectiveness of hyperbaric oxygen therapy in the treatment of complex regional pain syndrome. *J Int Med Res* 2004; 32: 258-62.
18. GU N, NIU JY, LIU WT *et al*.: Hyperbaric oxygen therapy attenuates neuropathic hyperalgesia in rats and idiopathic trigeminal neuralgia in patients. *Eur J Pain* 2012; 16: 1094-105.
19. YILDIZ S, KIRALP MZ, AKIN A *et al*.: A new treatment modality for fibromyalgia syndrome: hyperbaric oxygen therapy. *J Int Med Res* 2004; 32: 263-7.
20. EFRATI S, GOLAN H, BECHOR Y *et al*.: Hyperbaric oxygen therapy can diminish fibromyalgia syndrome - prospective clinical trial. *PLoS One* 2015; 10: e0127012.
21. LEWIS S: Pain: Microglia take control in chronic pain. *Nat Rev Neurosci* 2013; 14: 154-5.