GULF WAR ILLNESS

Neuroinflammation disorders exacerbated by environmental stressors.

O'Callaghan JP[1], Miller DB[2].

Metabolism. **2019 Nov**;100S:153951. doi: 10.1016/j.metabol.2019.153951. PMID: 31610852.

Neuroinflammation is a condition characterized by the elaboration of proinflammatory mediators within the central nervous system. Neuroinflammation has emerged as a dominant theme in contemporary neuroscience due to its association with neurodegenerative disease states such as Alzheimer's disease, Parkinson's disease and Huntington's disease. While neuroinflammation often is associated with damage to the CNS, it also can occur in the absence of neurodegeneration, e.g., in association with systemic infection. The "acute phase" inflammatory response to tissue injury or infections instigates neuroinflammation-driven "sickness behavior," i.e. a constellation of symptoms characterized by loss of appetite, fever, muscle pain, fatigue and cognitive problems. Typically, sickness behavior accompanies an inflammatory response that resolves quickly and serves to restore the body to homeostasis. However, recurring and sometimes chronic sickness behavior disorders can occur in the absence of an underlying cause or attendant neuropathology. Here, we review myalgic enchepalomyelitis/chronic fatigue syndrome (ME/CFS), Gulf War Illness (GWI), and chemobrain as examples of such disorders and propose that they can be exacerbated and perhaps initiated by a variety of environmental stressors. Diverse environmental stressors may disrupt the hypothalamic pituitary adrenal (HPA) axis and contribute to the degree and duration of a variety of neuroinflammation-driven diseases.

CHRONIC FATIGUE SYNDROME

Intra brainstem connectivity is impaired in chronic fatigue syndrome.

Barnden LR[1], Shan ZY[2], Staines DR[3], Marshall-Gradisnik S[4], Finegan K[5], Ireland T[6], Bhuta S[7].

Neuroimage Clin. **2019 Oct 19**;24:102045. doi: 10.1016/j.nicl.2019.102045. PMID: 31671321. [Epub ahead of print]

In myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS), abnormal MRI correlations with symptom severity and autonomic measures have suggested impaired nerve signal conduction within the brainstem. Here we analyse fMRI correlations to directly test connectivity within and from the brainstem. Resting and task functional MRI (fMRI) were acquired for 45 ME/CFS (Fukuda criteria) and 27 healthy controls (HC). We selected limited brainstem reticular activation system (RAS) regions-of-interest (ROIs) based on previous structural MRI findings in a different ME/CFS cohort (bilateral rostral medulla and midbrain cuneiform nucleus), the dorsal Raphe nucleus, and two subcortical ROIs (hippocampus subiculum and thalamus intralaminar nucleus) reported to have rich brainstem connections. When HC and ME/CFS were analysed separately, significant correlations were detected for both groups during both rest and task, with stronger correlations during task than rest. In ME/CFS, connections were absent between medulla and midbrain nuclei, although hippocampal connections with these nuclei were enhanced. When corresponding correlations from HC and ME/CFS were compared, ME/CFS connectivity deficits were detected within the brainstem between the medulla and cuneiform nucleus and between the brainstem and hippocampus and intralaminar thalamus, but only during task. In CFS/ME, weaker connectivity between some RAS nuclei was associated with increased symptom severity. RAS neuron oscillatory signals facilitate coherence in thalamo-cortical oscillations. Brainstem RAS connectivity deficits can explain autonomic changes and diminish cortical oscillatory coherence which can impair attention, memory, cognitive function, sleep quality and muscle tone, all symptoms of ME/CFS.

CHRONIC FATIGUE SYNDROME (Continued)

News and views in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): The role of co-morbidity and novel treatments.

Comhaire F[1], Deslypere JP[2].

Med Hypotheses. **2019 Oct 22**;134:109444. doi: 10.1016/j.mehy.2019.109444. PMID: 31669858. [Epub ahead of print]

Though affecting many thousands of patients, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) should be considered an orphan disease, since the cause remains elusive and no treatment is available that can provide complete cure. There is reasonable insight into the pathogenesis of signs and symptoms, and treatments specifically directed to immunological, inflammatory and metabolic processes offer relief to an increasing number of patients. Particular attention is given to the importance of co-morbidity requiring appropriate therapy. Promising results are obtained by treatment with Metformin, or possibly Momordica charantia extract, which will correct insulin resistance, with Meldonium improving the transportation of glucose into the mitochondria, with sodium dichloroacetate activating pyruvate dehydrogenase, and with nutraceutical support reducing oxidative and inflammatory impairment.

HEADACHE and MIGRAINE

Early Onset of Efficacy With Fremanezumab for the Preventive Treatment of Chronic Migraine.

Winner PK[1], Spierings ELH[2], Yeung PP[3], Aycardi E[3], Blankenbiller T[3], Grozinski-Wolff M[3], Yang R[3], Ma Y[3].

Headache. **2019 Nov 1**. doi: 10.1111/head.13654. PMID: 31675102. [Epub ahead of print]

OBJECTIVE: To assess the onset of efficacy for fremanezumab in chronic migraine by evaluating pain-related clinical measures at different time points.

BACKGROUND: Faster onset of efficacy of preventive treatments could benefit patients with migraine. Fremanezumab is a fully humanized monoclonal antibody that selectively targets calcitonin gene-related peptide, a neuropeptide involved in the pathophysiology of migraine. In 12-week clinical trials, subcutaneous fremanezumab significantly reduced the frequency of migraine headaches, headache hours, and headaches in general, without serious treatment-related adverse events. New drug classes of migraine preventive treatment demonstrate markedly different clinical profiles from standard-of-care treatments.

METHODS: In this double-blind phase III study, eligible patients were randomized 1:1:1 to receive subcutaneous injections of fremanezumab quarterly (675 mg at baseline, placebo at weeks 4 and 8), fremanezumab monthly (675 mg at baseline, 225 mg at weeks 4 and 8), or placebo at each time point. This study included secondary, exploratory, and post hoc analyses of the primary trial, evaluating the change in headache days of at least moderate severity or migraine days during the first 4 weeks of the trial.

RESULTS: A total of 1130 patients were randomized (fremanezumab quarterly, n = 376; fremanezumab monthly, n = 379; or placebo, n = 375). During the 4-week period after the first dose, the mean number of monthly headache days of at least moderate severity was reduced for the all-fremanezumab group (mean reduction [95% confidence interval]: -4.6 days [-5.1, -4.1]) compared with the placebo group (-2.3 days [-2.9, -1.6]; P < .0001). Treatment effects were observed at Week 1 for the all-fremanezumab group (-1.1 days [-1.3, -1.0]) vs placebo (-0.5 days [-0.7, -0.3]; P < .0001), with separation from placebo by Day 2 (P = .003). Similar effects were observed for the monthly average number of migraine days and mean number of monthly headache hours.

CONCLUSIONS: The early onset of efficacy of fremanezumab may have the potential to improve patient compliance and clinical outcomes.

HEADACHE and MIGRAINE (Continued)

Episodic primary migraine headache: prophylaxis with Pycnogenol® precents attacks and controls oxidative stress.

Cesarone MR[1], Dugall M[1], Hu S[1], Belcaro G[2], Hosoi M[1], Scipione V[1], Scipione C[1], Cotellese R[3].

Panminerva Med. **2019 Oct 25**. doi: 10.23736/S0031-0808.19.03745-5. PMID: 31670494. [Epub ahead of print]

BACKGROUND: The present registry study investigated effects of the dietary supplement Pycnogenol® on migraine headache attacks and oxidative stress in otherwise healthy subjects with migraine mild-moderate headache (MH) that were considered. To manage MH, these subjects used only a few drugs (anti-emetics, analgesics on demand) and lifestyle changes; only very occasionally they used other, more specific products such as triptans.

METHODS: Study GROUPS: one group used only standard management (SM), basically, management on demand. Oral magnesium and riboflavin (vitamin B2) were used with lipoic acid as they are considered useful to improve MH. Another group used the supplement Pycnogenol® (150 mg/day for 8 weeks) in addition to SM. These two groups were compared to a third (non-parallel, observational) group using topiramate (50 mg/day). If needed, subjects were allowed to use rescue medications.

RESULTS: 46 subjects were included in the study. 22 used the standard management and 24 were supplemented with Pycnogenol® in association with SM. In addition, 21 subjects were treated with topiramate. Safety with Pycnogenol® was very good. The two main management groups and the third non-parallel group had comparable baseline characteristics. The number of migraine attacks were significantly reduced during the observation period with Pycnogenol® ($p<0.05$) in comparison with SM. Supplementation was more effective in reducing the use of rescue medications ($p<0.05$) including analgesics compared to SM. At 8 weeks, the pain score was lower with Pycnogenol in comparison with SM ($p<0.05$). The working incapacity was significantly lower with Pycnogenol® than in the SM group ($P<0.05$). The number of migraine attacks was lower with topiramate compared to SM. Pain score, working incapacity and use of rescue medication were lower with topiramate than in SM. However, adverse effects with topiramate, included paresthesia, fatigue, dizziness and nausea even at low dosages complicated management. Some 50% of these side effects require a form of further treatment including medication. Oxidative stress: all included subjects had high oxidative stress at baseline. At 8 weeks, the level of plasma free radicals was significantly lowered with Pycnogenol® ($p<0.05$), but not in the SM or topiramate group.

CONCLUSIONS: In conclusion Pycnogenol® used as prophylaxis appears to reduce pain and the number and severity of symptoms in MH in parallel with a reduction on oxidative stress.

Effect of genetic liability to migraine on coronary artery disease and atrial fibrillation: a Mendelian randomization study.

Daghlas I[1,2], Guo Y[1,3], Chasman DI[1].

Eur J Neurol. **2019 Oct 29**. doi: 10.1111/ene.14111. PMID: 31661179. [Epub ahead of print]

BACKGROUND: Observational studies have implicated migraine as a risk factor for coronary artery disease (CAD) and atrial fibrillation (AF), however it is unclear whether migraine is causal in this relationship. We investigated potential causality between genetically instrumented liability to migraine and cardiovascular disease outcomes using two-sample Mendelian randomization.

METHODS: The exposure comprised 35 independent, genome-wide significant genetic variants identified in the largest published migraine GWAS (N_{cases} = 59,674 / $N_{controls}$ =316,078). The outcome datasets included GWAS of CAD (76,014 / 264,785), myocardial infarction (MI) (43,676 / 128,199), angina (10,618 / 326,065), and AF (60,620 / 970,216). MR estimates were generated using inverse-variance weighted random-effects meta-analysis, and further assessed with conventional MR sensitivity analyses.

RESULTS: We found evidence for a protective effect of migraine liability on CAD (odds ratio 0.86, 95% confidence interval 0.76-0.96, p=0.003), MI (0.86, 0.74-0.96, p=0.01), and angina (0.86, 0.75-0.99, p=0.04), but not on AF (1.00, 0.95-1.05, p=0.88). Analyses by migraine subtype showed an effect of migraine without aura on CAD risk (0.91, 0.84-0.99, p=0.014), but not of migraine with aura (1.00, 0.97-1.03, p=0.89). Sensitivity analyses indicated minimal bias by horizontal pleiotropy, outliers, reverse causality, or sample overlap.

CONCLUSIONS: We identified a potentially protective effect of genetically instrumented liability to migraine on CAD risk. Mechanistic research investigating this link is warranted.

HEADACHE and MIGRAINE (Continued)

Yoga for Treating Headaches: a Systematic Review and Meta-analysis.

Anheyer D[1], Klose P[2], Lauche R[3,4], Saha FJ[2], Cramer H[2,4].

J Gen Intern Med. **2019 Oct 30**. doi: 10.1007/s11606-019-05413-9. PMID: 31667736. [Epub ahead of print]

BACKGROUND: Headache disorders are currently the sixth leading cause of disability across the globe and therefore carry a significant disease burden. This systematic review and meta-analysis aims to investigate the effects of yoga on headache disorders.

METHODS: MEDLINE/PubMed, Scopus, the Cochrane Library, and PsycINFO were screened through May 2019. Randomized controlled trials (RCTs) were included when they assessed the effects of yoga in patients with a diagnosis of chronic or episodic headache (tension-type headache and/or migraine). Usual care (no specific treatment) or any active treatments were acceptable as control interventions. Primary outcome measures were headache frequency, headache duration, and pain intensity. For each outcome, standardized mean differences (SMD) and 95% confidence intervals (CI) were calculated.

RESULTS: Meta-analysis revealed a statistically significant overall effect in favor of yoga for headache frequency (5 RCTs; standardized mean difference (SMD) = - 1.97; 95% confidence interval (CI) - 2.75 to - 1.20; I^2 = 63.0%, τ^2 = 0.25, P = 0.03), headache duration (4 RCTs; SMD = - 1.45; 95% CI - 2.54 to - 0.37; I^2 = 69.0%, τ^2 = 0.33, P = 0.02), and pain intensity (5 RCTs; SMD = - 3.43; 95% CI - 6.08 to - 0.70, I^2 = 95.0%, τ^2 = 4.25, P < 0.01). The significant overall effect was mainly due to patients with tension-type headaches. For patients with migraine, no statistically significant effect was observed.

DISCUSSION: Despite discussed limitations, this review found preliminary evidence of short-term efficacy of yoga in improving headache frequency, headache duration, and pain intensity in patients suffering from tension-type headaches. Further studies are urgently needed to draw deeper conclusions from the available results.

Migraine-associated gene expression in cell types of the central and peripheral nervous system.

Vgontzas A[1], Renthal W[1].

Cephalalgia. **2019 Oct 29**:333102419877834. doi: 10.1177/0333102419877834. PMID: 31660761. [Epub ahead of print]

BACKGROUND: Genome-wide association studies have implicated dozens of genes with migraine susceptibility, but it remains unclear in which nervous system cell types these genes are expressed.

METHODS: Using single-cell RNA sequencing data from the central and peripheral nervous system, including the trigeminal ganglion, the expression of putative migraine-associated genes was compared across neuronal, glial and neurovascular cell types within these tissues.

RESULTS: Fifty-four putative migraine-associated genes were expressed in the central nervous system, peripheral nervous system or neurovascular cell types analyzed. Six genes (11.1%) were selectively enriched in central nervous system cell types, three (5.5%) in neurovascular cell types, and two (3.7%) in peripheral nervous system cell types. The remaining genes were expressed in multiple cell types.

CONCLUSIONS: Single-cell RNA sequencing of the brain and peripheral nervous system localizes each migraine-associated gene to its respective nervous system tissue and the cell types in which it is expressed. While the majority of migraine-associated genes are broadly expressed, we identified several cell-type-specific migraine-associated genes in the central nervous system, peripheral nervous system, and neurovasculature.

TRIAL REGISTRATION: not applicable.

Targeting calcitonin gene-related peptide: a new era in migraine therapy.

Charles A[1], Pozo-Rosich P[2].

Lancet. **2019 Oct 23**. pii: S0140-6736(19)32504-8. doi: 10.1016/S0140-6736(19)32504-8. PMID: 31668411.

Migraine is one of the most prevalent and disabling diseases worldwide, but until recently, few migraine-specific therapies had been developed. Extensive basic and clinical scientific investigation has provided strong evidence that the neuropeptide calcitonin gene-related peptide (CGRP) has a key role in migraine. This evidence led to the development of small molecule CGRP receptor antagonists and monoclonal antibodies targeting either CGRP or its receptor. Clinical trials investigating these therapies have consistently shown statistically significant efficacy for either the acute or preventive treatment of migraine. No serious safety or tolerability issues have been identified in the trials of the monoclonal antibody therapies. Although the appropriate place of these new migraine-specific therapies relative to other available acute and preventive treatments remains to be determined, a growing body of evidence shows that therapeutic approaches targeting CGRP have the potential to transform the clinical management of migraine.

CHRONIC PAIN

Virtual Reality as a Therapy Adjunct for Fear of Movement in Veterans With Chronic Pain: Single-Arm Feasibility Study.

Fowler CA[1], Ballistrea LM[1], Mazzone KE[2], Martin AM[2], Kaplan H[3], Kip KE[1,4], Ralston K[1], Murphy JL[2,5], Winkler SL[1].

JMIR Form Res. **2019 Oct 30**;3(4):e11266. doi: 10.2196/11266. PMID: 31670696.

BACKGROUND: Virtual reality (VR) has demonstrated efficacy for distraction from pain-related thoughts and exposure to feared movements. Little empirical VR research has focused on chronic pain management.

OBJECTIVE: The purpose of this study was to examine the feasibility of VR as an adjunctive intervention for Veterans with chronic pain. We designed a hierarchy ranging from low-intensity pain distraction to high-intensity movement-based exposure for this purpose. VR apps were mapped onto the hierarchy.

METHODS: Sixteen Veterans receiving inpatient chronic pain rehabilitation participated in daily VR sessions over a 3-week period. Trajectories across the distraction-to-exposure hierarchy and Veteran-reported intensity ratings were described and evaluated over time. Minimum clinically important differences (MCIDs), pre-post effect sizes, and 95% confidence intervals were examined for fear of movement using the Fear of Daily Activities Questionnaire (FDAQ) and Pain Outcomes Questionnaire-VA (POQ-VA; fear scale). This approach was applied to secondary outcomes: POQ-VA (pain intensity, interference, negative affect), Pain Catastrophizing Scale, and Patient-Specific Functioning Scale (PSFS). Session attendance, completion, and VR experiences were described.

RESULTS: Ten of 14 Veterans (71%) who participated in three or more VR sessions completed the distraction-to-exposure hierarchy. Only three trajectories emerged more than once. Due to high completion rates, Veterans that completed the hierarchy could self-select nonhierarchy apps. Veterans rated all hierarchy levels (low, medium, high) near medium intensity. Self-selected activities were rated as high intensity. For kinesiophobia, six Veterans (38%) exceeded the MCID on the FDAQ and a small effect size improvement was observed (Cohen d=-0.35). The confidence interval (95% CI -0.71 to 0.01) indicated the possibility of a null effect. The POQ-VA fear scale yielded no effect (Cohen d=0.06, 95% CI -0.43 to 0.54). For secondary outcomes, Veterans exceeding MCID were calculated with complete data: pain intensity (1/15, 7%), pain catastrophizing (5/14, 36%), and patient-specific functioning (10/15, 67%). Effect sizes were large for patient-specific functioning (Cohen d=1.14, 95% CI 0.50-1.78), medium for mobility interference (Cohen d=-0.56, 95% CI -0.96 to -0.16), and small for pain intensity (Cohen d=-0.40, 95% CI -0.69 to -0.12) and catastrophizing (Cohen d=-0.41, 95% CI -0.79 to -0.02). No effects were observed for interference in daily activities (Cohen d=0.10, 95% CI -0.27 to 0.47) and negative affect (Cohen d=0.07, 95% CI -0.26 to 0.40). Veterans attended 85.2% (98/108) of VR sessions and completed 95% (93/96) of sessions attended. Twenty-minute sessions were rated as too short. No significant adverse events were reported.

CONCLUSIONS: Findings support the feasibility of VR as an adjunct for Veterans with chronic pain. However, the hierarchy will require modification, as evidenced by homogeneous intensity ratings. Veteran-selected activities presented the highest intensity ratings, largest outcome effect size (PSFS), and MCID. This highlights the important role of utilizing Veteran stakeholders in hierarchy modification, design of VR interventions, and outcome selection.

The role of positive goal engagement in increased mental well-being among individuals with chronic non-cancer pain.

Iddon JE[1], Taylor PJ[2], Unwin J[3], Dickson JM[4,5] .

Br J Pain. **2019 Nov**;13(4):230-238. doi: 10.1177/2049463718824857. PMCID: PMC6791052. PMID: 31656629.

Individuals with chronic pain commonly report significant functional impairment and reduced quality of life. Despite this, little is known about psychological processes and mechanisms underpinning enhancements in well-being within this population. The study aimed to investigate whether (1) increased levels of pain intensity and interference were associated with lower levels of mental well-being, (2) increased positive goal engagement was associated with higher levels of mental well-being and (3) whether the relationships between pain characteristics and mental well-being were mediated by increased positive goal engagement. A total of 586 individuals with chronic pain participated in the cross-sectional, online study. Participants completed self-report measures to assess pain intensity and interference, mental well-being and goal motivation variables. Results showed that pain interference and positive goal engagement were associated with mental well-being. Moreover, the relationship between pain interference and mental well-being was partially mediated by positive goal engagement. The results provide tentative evidence for the protective role of positive goal engagement in enabling individuals with chronic pain to maintain a sense of mental well-being. The study develops the biopsychosocial model of chronic pain by examining the roles and relationships of relevant yet previously unexplored psychological constructs. The promotion of mental well-being through the enhancement of positive goal engagement is discussed, offering a platform for further research and clinical interventions.

CHRONIC PAIN (Continued)

Yoga, Physical Therapy, and Back Pain Education for Sleep Quality in Low-Income Racially Diverse Adults with Chronic Low Back Pain: a Secondary Analysis of a Randomized Controlled Trial.

Roseen EJ[1,2], Gerlovin H[3], Femia A[4], Cho J[4], Bertisch S[5,6], Redline S[5,6], Sherman KJ[7,8], Saper R[4].

J Gen Intern Med. **2019 Oct 30**. doi: 10.1007/s11606-019-05329-4. PMID: 31667747. [Epub ahead of print]

BACKGROUND: Poor sleep is common among adults with chronic low back pain (cLBP), but the influence of cLBP treatments, such as yoga and physical therapy (PT), on sleep quality is under studied.

OBJECTIVE: Evaluate the effectiveness of yoga and PT for improving sleep quality in adults with cLBP.

DESIGN: Secondary analysis of a randomized controlled trial.

SETTING: Academic safety-net hospital and 7 affiliated community health centers.

PARTICIPANTS: A total of 320 adults with cLBP.

INTERVENTION: Twelve weekly yoga classes, 1-on-1 PT sessions, or an educational book.

MAIN MEASURES: Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI) global score (0-21) at baseline, 12 weeks, and 52 weeks. Additionally, we also evaluated how the proportion of participants who achieved a clinically meaningful improvement in sleep quality (> 3-point reduction in PSQI) at 12 weeks varied by changes in pain and physical function at 6 weeks.

KEY RESULTS: Among participants (mean age = 46.0, 64% female, 82% non-white), nearly all (92%) reported poor sleep quality (PSQI > 5) at baseline. At 12 weeks, modest improvements in sleep quality were observed among the yoga (PSQI mean difference [MD] = - 1.19, 95% confidence interval [CI] - 1.82, - 0.55) and PT (PSQI MD = - 0.91, 95% CI - 1.61, - 0.20) groups. Participants who reported a ≥ 30% improvement in pain or physical function at 6 weeks, compared with those who improved < 10%, were more likely to be a sleep quality responder at 12 weeks (odds ratio [OR] = 3.51, 95% CI 1.73, 7.11 and OR = 2.16, 95% CI 1.18, 3.95, respectively). Results were similar at 52 weeks.

CONCLUSION: In a sample of adults with cLBP, virtually all with poor sleep quality prior to intervention, modest but statistically significant improvements in sleep quality were observed with both yoga and PT. Irrespective of treatment, clinically important sleep improvements at the end of the intervention were associated with mid-intervention pain and physical function improvements.

TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT01343927.

Emerging Roles of Long Non-coding RNAs in Chronic Neuropathic Pain.

Wu W[1], Ji X[2], Zhao Y[3].

Front Neurosci. **2019 Oct 18**;13:1097. doi: 10.3389/fnins.2019.01097. PMCID: PMC6813851. PMID: 31680832.

Chronic neuropathic pain, a type of chronic and potentially disabling pain caused by a disease or injury of the somatosensory nervous system, spinal cord injury, or various chronic conditions, such as viral infections (e.g., post-herpetic neuralgia), autoimmune diseases, cancers, and metabolic disorders (e.g., diabetes mellitus), is one of the most intense types of chronic pain, which incurs a major socio-economic burden and is a serious public health issue, with an estimated prevalence of 7-10% in adults throughout the world. Presently, the available drug treatments (e.g., anticonvulsants acting at calcium channels, serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants, opioids, topical lidocaine, etc.) for chronic neuropathic pain patients are still rare and have disappointing efficacy, which makes it difficult to relieve the patients' painful symptoms, and, at best, they only try to reduce the patients' ability to tolerate pain. Long non-coding RNAs (lncRNAs), a type of transcript of more than 200 nucleotides with no protein-coding or limited capacity, were identified to be abnormally expressed in the spinal cord, dorsal root ganglion, hippocampus, and prefrontal cortex under chronic neuropathic pain conditions. Moreover, a rapidly growing body of data has clearly pointed out that nearly 40% of lncRNAs exist specifically in the nervous system. Hence, it was speculated that these dysregulated lncRNAs might participate in the occurrence, development, and progression of chronic neuropathic pain. In other words, if we deeply delve into the potential roles of lncRNAs in the pathogenesis of chronic neuropathic pain, this may open up new strategies and directions for the development of novel targeted drugs to cure this refractory disorder. In this article, we primarily review the status of chronic neuropathic pain and provide a general overview of lncRNAs, the detailed roles of lncRNAs in the nervous system and its related diseases, and the abnormal expression of lncRNAs and their potential clinical applications in chronic neuropathic pain. We hope that through the above description, readers can gain a better understanding of the emerging roles of lncRNAs in chronic neuropathic pain.

CHRONIC PAIN (Continued)

The interplay of exercise, placebo and nocebo effects on experimental pain.

Colloca L[1,2,3], Corsi N[4,5], Fiorio M[5].

Sci Rep. **2018 Oct 3**;8(1):14758. doi: 10.1038/s41598-018-32974-2. PMCID: PMC6170492. PMID: 30283022.

[Note: Delayed posting in PubMed—Not previously listed in RAC Research Alerts.]

Over the last few decades, placebo, and nocebo effects in general, have been investigated at rest. This proposed study explores whether they could work even when the experience of pain occurs during a movement. Exercise itself can have a hypoalgesic effect, suggesting that placebo- and exercise-induced hypoalgesia could foster pain reduction. In the present study, we investigated the interplay of exercise, placebo and nocebo effects on pain. To this aim, we developed a machine-controlled isotonic motor task to standardize the exercise across participants and used a well-validated model of placebo and nocebo manipulations with reinforced expectations via a conditioning procedure including visual cues paired with heat painful stimulations. Participants reported expectations and pain on a trial-by-trial basis. We found that the standardized isotonic exercise elicited a reduction of pain intensity. Moreover, both exercise and placebo induced comparable hypoalgesic effects. When the exercise was added, placebo and nocebo effects were influenced by expectations but were not affected by fatigue or sex differences. Exercise-, placebo- and nocebo-induced pain modulation are likely to work through distinct mechanisms and neurophysiological research is needed to fully exploit the implications for sport, rehabilitation and pain management.

IRRITABLE BOWEL SYNDROME

Duodenal and rectal mucosal microbiota related to small intestinal bacterial overgrowth in diarrhea-predominant irritable bowel syndrome.

Yang M[1], Zhang L[1], Hong G[1], Li Y[1], Li G[1], Qian W[1], Xiong H[1], Bai T[1], Song J[1], Hou X[1].

J Gastroenterol Hepatol. **2019 Oct 31**. doi: 10.1111/jgh.14910. PMID: 31674052. [Epub ahead of print]

BACKGROUND AND AIM: Small intestinal bacterial overgrowth (SIBO) has been proposed as an etiologic factor in irritable bowel syndrome, particularly the diarrhea-predominant subtype (IBS-D). We aimed to identify potential intestinal microbial pattern in IBS-D patients with SIBO.

METHODS: Diarrhea-predominant irritable bowel syndrome patients fulfilling Rome III criteria were recruited and randomly divided into an exploratory cohort (57 cases) and a validation cohort (20 cases). SIBO was identified according to standard glucose hydrogen breath test. For 16S rRNA gene sequencing, samples of duodenal mucosa, duodenal fluid, rectal mucosa, and fresh feces were collected and performed. The α and β diversity, as well as differences in microbial composition and function, in $SIBO^+$ and $SIBO^-$ IBS-D subjects were evaluated.

RESULTS: The microbial diversity and composition obviously differed between $SIBO^+$ and $SIBO^-$ IBS-D in duodenal and rectal mucosa but not in duodenal fluid and fresh feces. For rectal mucosal microbiota, it displayed markedly reduced aerobe and Gram-negative bacteria and increased facultative anaerobe and Gram-positive bacteria, moreover, altered functions of microbial metabolism in $SIBO^+$ IBS-D. Significantly higher rectal mucosa-related microbial dysbiosis index was observed in $SIBO^+$ IBS-D, and a cut-off value at -0.37 had a sensitivity of 56.55% and specificity of 90.91% to identify the SIBO in IBS-D subjects.

CONCLUSIONS: Mucosal microbiota, rather than luminal bacteria, has a more apparent dysbiosis in $SIBO^+$ IBS-D patients relative to those without SIBO. Rectal mucosa-associated microbiota may act as a potential predictor of SIBO in IBS-D patients.

IRRITABLE BOWEL SYNDROME (Continued)

Does the Microbiota Play a Pivotal Role in the Pathogenesis of Irritable Bowel Syndrome?

Fagoonee S[1], Pellicano R[2].

J Clin Med. **2019 Oct 30**;8(11). pii: E1808. doi: 10.3390/jcm8111808. PMCID: PMC6912670. PMID: 31671546.

Excerpt: The microbial community that lives in the human body, called the microbiota, consists of a large variety of microorganisms including bacteria, viruses, fungi, eukaryotes and archae. Every human being harbors between 10 trillion and 100 trillion microbial cells, which is approximately equal to 10 times the total number of body cells. The term microbiome refers to the gene set of these microbial cells. The gut microbiome is estimated to contain over 150 times more genes than the human genome [1]. During long-standing interactions, a mutual co-evolution between gut microbiota and the host occurs, with the former making an important contribution to human metabolism, with significant effects on the anatomical, physiological, and immunological development of the host [2,3]. Considering that many bacterial species still cannot be cultured, our understanding of gut microbiota has evolved over the past few years thanks to the availability of advanced molecular methods that permit us to identify a large quantity of microorganisms [4]. Today, it is known that although 98% of the gut microbiota is composed of four phyla of bacteria (Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria), the majority are either Firmicutes or Bacteroidetes [4,5]. With this premise, in the last decade, the gut microbiota has become a key topic in the investigation of several gastrointestinal (GI) as well as extra-GI diseases [6,7,8,9].

Irritable bowel syndrome (IBS) is a common functional clinical condition characterized by abdominal discomfort or pain and alteration of gut habits without an underlying structural pathology [10]. As IBS affects 9–23% of the general population [11], with considerable impact on quality of life and health care resource utilization, it represents an important medical challenge in term of diagnosis and treatment [12]. The pathogenesis of IBS remains unclear, with several factors supposed to be involved, including environmental and host factors such as psychosocial stressors, food intolerance, antibiotics, enteric infections, altered pain perception, altered brain–gut interactions, dysbiosis (imbalance within the bacterial community), increased intestinal permeability, increased gut mucosal immune activation and visceral hypersensitivity [13].

In recent years, the relationship between gut microbiota and brain–gut interactions in the pathogenesis of IBS has become a key topic in clinical and biomedical research. This issue has been accurately discussed in a recent review by Quigley [14]. Beginning with an excursus on the historical steps that led to the definition of the gut–brain axis, the author discussed the modern theory that postulates the involvement of gut microbiota in both the gut–brain axis and IBS. On the basis of this theory, the pathogenesis of IBS would be related to the action of central stimuli, such as stress, that could disrupt mucosal immunity, reduce microbial diversity and alter gut barrier function, leading to gut dysfunction. Although much work still needs to be done, there is evidence to support this pathogenetic model.

[See full text and references of article in Journal of Clinical Medicine.]

OTHER RESEARCH OF INTEREST

Effects of attachment-based compassion therapy (ABCT) on brain-derived neurotrophic factor and low-grade inflammation among fibromyalgia patients: A randomized controlled trial.

Montero-Marin J[1], Andrés-Rodríguez L[2,3,4,5], Tops M[6], Luciano JV[2,3,4], Navarro-Gil M[7], Feliu-Soler A[2,3,4], López-Del-Hoyo Y[8], Garcia-Campayo J[2,9].

Sci Rep. **2019 Oct 30**;9(1):15639. doi: 10.1038/s41598-019-52260-z. PMID: 31666651.

Fibromyalgia (FM) is a disabling syndrome characterized by chronic pain associated with fatigue. Its pathogenesis is unknown, but alterations in central sensitization, involving an imbalance of brain-derived neurotrophic factor (BDNF) and inflammatory biomarkers, appear to be implicated. The aim of this study was to evaluate the impact of attachment-based compassion therapy (ABCT) on levels of BDNF, the inflammatory markers TNF-α, IL-6, IL-10, and the C-reactive protein (CRP), analysing whether biomarkers play a mediating/moderating role in improvements in FM functional status. Thirty-four female patients with FM participated in a RCT and were assigned to ABCT or relaxation therapy. Blood extractions were conducted at baseline and post-intervention, with self-report assessments of functional status (FIQ) at baseline, post-intervention and 3-month follow-up. A pro-inflammatory composite was obtained by summing up IL-6, TNF-α and CRP normalized values. Non-parametric tests, analysis of variance and regression models were used to evaluate treatment and mediation/moderation. Compared to relaxation therapy, ABCT showed significant improvements in FIQ and decreases in BDNF, CRP, and pro-inflammatory composite. Changes in BDNF had a mediating role in FIQ. ABCT seems to reduce BDNF and appears to have anti-inflammatory effects in FM patients. Reductions in BDNF could be a mechanism of FM functional status improvement. Clinical Trial Registration: http://ClinicalTrials.gov, identifier NCT02454244. Date: May 27th, 2015.

OTHER RESEARCH OF INTEREST (Continued)

Protein intake and amino acid supplementation regulate exercise recovery and performance through the modulation of mTOR, AMPK, FGF21, and immunity.

Torre-Villalvazo I[1], Alemán-Escondrillas G[1], Valle-Ríos R[2], Noriega LG[3].

Nutr Res. **2019 Jul 2**. pii: S0271-5317(19)30135-6. doi: 10.1016/j.nutres.2019.06.006. PMID: 31672317. [Epub ahead of print]

[Note: Delayed posting in PubMed—Not previously listed in RAC Research Alerts.]

Exercise is considered to be the best approach to improve quality of life, and together with a healthy and adequate dietary pattern, exercise represents the best strategy to reduce the risk of chronic metabolic and inflammatory diseases, such as those related to obesity. The regularity and intensity of exercise is modulated at the molecular level in the skeletal muscle by two protein kinases, the mechanistic target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK), which act as sensors of external stimuli, showing the energy status of muscular fibers. The mTOR pathway is activated by insulin and amino acid availability, and its metabolic actions culminate in increased protein synthesis and reduced autophagy, leading to an increase in muscle mass. In contrast, AMPK activation induces a transcriptional program aimed to increase the mitochondrial content in skeletal muscle, transforming fast-twitch glycolytic fibers to slow-twitch oxidative fibers and increasing resistance to fatigue. In addition, inadequate exercise training induces imbalance in the immune response, generating excessive inflammation and/or immunosuppression. The purpose of this review is to summarize recent studies that provide insight into dietary protein interventions and/or amino acid supplementation that may improve outcomes after exercise by modulating 1) mTOR and AMPK activation during early exercise recovery, leading to increased muscle protein synthesis or increased oxidative capacity; 2) undesirable inflammatory responses; and 3) fibroblast growth factor 21 (FGF21) levels that may have relevant implications in skeletal muscle metabolism, particularly during the exercise recovery and performance of obese subjects.

Neuropsychiatric Implications of Chronic Lead Exposure.

Cassleman KL[1], Dorrance KA[2], Todd AC[3].

Mil Med. **2019 Oct 31**. pii: usz362. doi: 10.1093/milmed/usz362. PMID: 31670374. [Epub ahead of print]

There is growing awareness of chronic exposures to lead, with recent evidence indicating that there is an increased risk of a range of health effects that include cardiovascular, kidney, cognitive, and premature mortality, at blood levels lower than what was previously considered elevated. This report describes the case of a 42-year-old active duty officer with a history of anxiety, cognitive impairment, and paroxysmal hypertensive episodes associated with elevated body burdens of lead as measured in bone, while having low or unremarkable blood level measurements. Challenges related to work-up, treatments, and outcomes are discussed. An elevated body burden of lead may contribute to increased irritability, fatigue, and anxiety, mimicking posttraumatic stress disorder and other primary psychiatric conditions. This presentation highlights the need for an increased index of suspicion of lead poisoning in both medical and psychiatric care, particularly in military populations.

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