GULF WAR ILLNESS

Do Gulf War veterans with high levels of deployment-related exposures display symptoms suggestive of Parkinson's disease?

Chao L.[1,2,3].

Int J Occup Med Environ Health. **2019 Jul 15**;32(4):503–526. doi: 10.13075/ijomeh.1896.01346. PMID: 31309787.

Objectives: Veterans of the 1991 Gulf War (GW) were exposed to a myriad of potentially hazardous chemicals during deployment. Epidemiological data suggest a possible link between chemical exposures and Parkinson's disease (PD); however, there have been no reliable data on the incidence or prevalence of PD among GW veterans to date. This study included the following 2 questions: 1. Do deployed GW veterans display PD-like symptoms? and 2. Is there a relationship between the occurrence and quantity of PD-like symptoms, and the levels of deployment-related exposures in GW veterans?

Material and Methods: Self-reports of symptoms and exposures to deployment-related chemicals were filled out by 293 GW veterans, 202 of whom had undergone 3 Tesla volumetric measurements of basal ganglia volumes. Correlation analyses were used to examine the relationship between the frequency of the veterans' self-reported exposures to deployment-related chemicals, motor and non-motor symptoms of PD, and the total basal ganglia volumes.

Results: Healthy deployed GW veterans self-reported few PD-like non-motor symptoms and no motor symptoms. In contrast, GW veterans with Gulf War illness (GWI) self-reported more PD-like motor and non-motor symptoms, and more GW-related exposures. Compared to healthy deployed veterans, those with GWI also had lower total basal ganglia volumes.

Conclusions: Although little is known about the long-term consequences of GWI, findings from this study suggest that veterans with GWI show more symptoms as those seen in PD/prodromal PD, compared to healthy deployed GW veterans. Int J Occup Med Environ Health. 2019;32(4):503–26

CHRONIC FATIGUE SYNDROME

Current Research Provides Insight into the Biological Basis and Diagnostic Potential for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

Sweetman E[1], Noble A[1], Edgar C[1], Mackay A[1], Helliwell A[1], Vallings R[2], Ryan M[3], Tate W[4].

Diagnostics (Basel). **2019 Jul 10**;9(3). pii: E73. doi: 10.3390/diagnostics9030073. PMID: 3129593.

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a severe fatigue illness that occurs most commonly following a viral infection, but other physiological triggers are also implicated. It has a profound long-term impact on the life of the affected person. ME/CFS is diagnosed primarily by the exclusion of other fatigue illnesses, but the availability of multiple case definitions for ME/CFS has complicated diagnosis for clinicians. There has been ongoing controversy over the nature of ME/CFS, but a recent detailed report from the Institute of Medicine (Academy of Sciences, USA) concluded that ME/CFS is a medical, not psychiatric illness. Importantly, aspects of the biological basis of the ongoing disease have been revealed over the last 2-3 years that promise new leads towards an effective clinical diagnostic test that may have a general application. Our detailed molecular studies with a preclinical study of ME/CFS patients, along with the complementary research of others, have reported an elevation of inflammatory and immune processes, ongoing neuro-inflammation, and decreases in general metabolism and mitochondrial function for energy production in ME/CFS, which contribute to the ongoing remitting/relapsing etiology of the illness. These biological changes have generated potential molecular biomarkers for use in diagnostic ME/CFS testing.

CHRONIC FATIGUE SYNDROME (Continued)

MicroRNAs as biomarkers of pain intensity in patients with chronic fatigue syndrome.

Al-Rawaf HA[1,2], Alghadir AH[1], Gabr SA[1].

Pain Pract. **2019 Jul 8**. doi: 10.1111/papr.12817. PMID: 31282597. [Epub ahead of print]

BACKGROUND: Numerous experimental models have shown that microRNAs play an important role in regulating pain-processing in clinical pain disorders. In this study, we evaluated a set of micro-RNAs as diagnostic biomarkers of pain intensity in adolescents with chronic fatigue syndrome (CFS). We then correlated the expression of these microRNAs with the levels of inflammatory markers and pain-related comorbidities in adolescents with CSF and healthy controls (HCs).

METHODS: A total of 150 adolescents, aged 12-18 years, participated in this study between April 2016 and April 2017. The participants were classified into two groups: adolescents with CFS (n=100) and HCs (n=50). RT-PCR was used to evaluate the expression of miR-558, miR-146a, miR-150, miR-124, and miR-143. Immunoassay analysis was used to assess the levels of immune inflammatory markers IL-6, TNF-α, and COX-2.

RESULTS: Adolescents with CFS showed significantly higher pain thresholds than comparable non-fatigued HCs. Also, enjoy of life and relation to others as the life domains, showed lower pain interference in CFS patients. Differential expression of miR-558, miR-146a, miR-150, miR-124, and miR-143 was significantly down regulated and notably interfered with pain intensity and frequency in patients with CFS. Also, the expression of these miRNAs was significantly correlated with that of IL-6, TNF-α, and COX-2, which have been shown to mediate pain intensity in patients with CFS. Girls with CSF showed significantly decreased expression levels of these miRNAs compared with the levels of boys with CSF. Girls with CSF also showed increased expression of inflammatory pain-related markers IL-6, TNF-α, and COX-2, compared with the levels of boys with CSF.

CONCLUSIONS: The intensity and consequences of pain were influenced by differential expression of miR-558, miR-146a, miR-150, miR-124, and miR-143, which was directly, associated with higher expression of immune inflammatory related genes TNFα, IL-6, and COX-2 in adolescences with CFS. Further studies of larger patient cohorts will help clarify the role of miRNAs in the pathogenesis of CFS.

HEADACHE and MIGRAINE

A prospective study of migraine history and venous thromboembolism in older adults.

Folsom AR[1], Lutsey PL[1], Misialek JR[1], Cushman M[2,3].

Res Pract Thromb Haemost. **2019 Apr 3**;3(3):357-363. doi: 10.1002/rth2.12200. PMCID: PMC6611375. PMID: 31294322. eCollection 2019 Jul.

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

Background: Limited evidence suggests that migraine might be a risk factor for venous thromboembolism (VTE). We conducted an epidemiologic study to assess whether migraine history is associated prospectively with VTE or cross sectionally with hemostatic risk markers for VTE.

Methods: In a population-based US cohort, 11 985 participants free of VTE reported headache symptoms in 1993-1995. We classified participants as having either migraines with or without aura, severe nonmigraine headaches, or no severe headaches. We followed them through 2015 for incident VTE verified by medical records.

Results: Participants' mean age at baseline was 60 years (SD: 6). Eleven percent were classified as having a migraine history (932 without aura and 396 with aura). Over a mean of 18 years and 211 913 person-years at risk, 688 participants developed VTE. Participants with a migraine history had no greater risk of VTE compared with those free of severe headache (adjusted hazard ratio [HR]: 1.06, 95% confidence interval [CI]: 0.82-1.36). Those with migraine history with aura had an HR of 1.25 (95% CI: 0.85-1.85). Self-reported physician diagnosis of migraine carried an HR of 1.22 (0.96-1.55). At baseline, those with a history of migraine, furthermore, did not have a higher frequency of elevated hemostatic risk factors or a higher genetic risk score for VTE.

Conclusion: This study does not support the hypothesis that migraine history is an important risk factor for VTE in older adults.

HEADACHE and MIGRAINE (Continued)

Rimegepant, an Oral Calcitonin Gene-Related Peptide Receptor Antagonist, for Migraine.

Lipton RB[1], Croop R[1], Stock EG[1], Stock DA[1], Morris BA[1], Frost M[1], Dubowchik GM[1], Conway CM[1], Coric V[1], Goadsby PJ[1].

N Engl J Med. **2019 Jul 11**;381(2):142-149. doi: 10.1056/NEJMoa1811090. PMID: 31291516.

BACKGROUND: Calcitonin gene-related peptide receptor has been implicated in the pathogenesis of migraine. Rimegepant is an orally administered, small-molecule, calcitonin gene-related peptide receptor antagonist that may be effective in acute migraine treatment.

METHODS: In a multicenter, double-blind, phase 3 trial, we randomly assigned adults with at least a 1-year history of migraine and two to eight migraine attacks of moderate or severe intensity per month to receive rimegepant orally at a dose of 75 mg or matching placebo for the treatment of a single migraine attack. The primary end points were freedom from pain and freedom from the most bothersome symptom (other than pain) identified by the patient, both of which were assessed 2 hours after the dose of rimegepant or placebo was administered.

RESULTS: A total of 1186 patients were randomly assigned to receive rimegepant (594 patients) or placebo (592 patients); of these, 537 patients in the rimegepant group and 535 patients in the placebo group could be evaluated for efficacy. The overall mean age of the patients evaluated for efficacy was 40.6 years, and 88.7% were women. In a modified intention-to-treat analysis, the percentage of patients who were pain-free 2 hours after receiving the dose was 19.6% in the rimegepant group and 12.0% in the placebo group (absolute difference, 7.6 percentage points; 95% confidence interval [CI], 3.3 to 11.9; P<0.001). The percentage of patients who were free from their most bothersome symptom 2 hours after the dose was 37.6% in the rimegepant group and 25.2% in the placebo group (absolute difference, 12.4 percentage points; 95% CI, 6.9 to 17.9; P<0.001). The most common adverse events were nausea and urinary tract infection.

CONCLUSIONS: Treatment of a migraine attack with the oral calcitonin gene-related peptide receptor antagonist rimegepant resulted in a higher percentage of patients who were free of pain and free from their most bothersome symptom than placebo. (Funded by Biohaven Pharmaceuticals; ClinicalTrials.gov number, NCT03237845.).

Microstructural white matter changes preceding white matter hyperintensities in migraine.

Arkink EB[1], Palm-Meinders IH[1], Koppen H[1], Milles J[1], van Lew B[1], Launer LJ[1], Hofman PAM[1], Terwindt GM[1], van Buchem MA[1], Ferrari MD[1], Kruit MC[2].

Neurology. **2019 Jul 11**. pii: 10.1212/WNL.0000000000007940. doi: 10.1212/WNL.0000000000007940. PMID: 31296653. [Epub ahead of print]

OBJECTIVE: We used magnetization transfer imaging to assess white matter tissue integrity in migraine, to explore whether white matter microstructure was more diffusely affected beyond visible white matter hyperintensities (WMHs), and to explore whether focal invisible microstructural changes precede visible focal WMHs in migraineurs.

METHODS: We included 137 migraineurs (79 with aura, 58 without aura) and 74 controls from the Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA) study, a longitudinal population-based study on structural brain lesions in migraine patients, who were scanned at baseline and at a 9-year follow-up. To assess microstructural brain tissue integrity, baseline magnetization transfer ratio (MTR) values were calculated for whole brain white matter. Baseline MTR values were determined for areas of normal-appearing white matter (NAWM) that had progressed into MRI-detectable WMHs at follow-up and compared to MTR values of contralateral NAWM.

RESULTS: MTR values for whole brain white matter did not differ between migraineurs and controls. In migraineurs, but not in controls, NAWM that later progressed to WMHs at follow-up had lower mean MTR (mean [SD] 0.354 [0.009] vs 0.356 [0.008], p = 0.047) at baseline as compared to contralateral white matter.

CONCLUSIONS: We did not find evidence for widespread microstructural white matter changes in migraineurs compared to controls. However, our findings suggest that a gradual or stepwise process might be responsible for evolution of focal invisible microstructural changes into focal migraine-related visible WMHs.

HEADACHE and MIGRAINE (Continued)

Fluctuating regional brainstem diffusion imaging measures of microstructure across the migraine cycle.

Marciszewski KK[1], Meylakh N[1], Pietro FD[1], Macefield VG[2], Macey PM[3], Henderson LA[4].

eNeuro. **2019 Jul 12**. pii: ENEURO.0005-19.2019. doi: 10.1523/ENEURO.0005-19.2019. PMID: 31300542. [Epub ahead of print]

The neural mechanisms responsible for the initiation and expression of migraines remain unknown. Though there is growing evidence of changes in brainstem anatomy and function between attacks, very little is known about brainstem function and structure in the period immediately prior to a migraine. The aim of this investigation is to use brainstem-specific analyses of diffusion weighted images to determine if the brainstem pain processing regions display altered structure in individuals with migraine across the migraine cycle, and in particular immediately prior to a migraine. Diffusion tensor images (29 controls, 36 migraineurs) were used to assess brainstem anatomy in migraineurs compared with controls. We found that during the interictal phase, migraineurs displayed greater mean diffusivity in the region of the spinal trigeminal nucleus, dorsomedial/dorsolateral pons and midbrain periaqueductal gray matter/cuneiform nucleus. Remarkably, the mean diffusivity returned to controls levels during the 24-hour period immediately prior to a migraine, only to increase again within the three following days. Additionally, fractional anisotropy was significantly elevated in the region of the medial lemniscus/ventral trigeminal thalamic tract in migraineurs compared with controls over the entire migraine cycle. These data show that regional brainstem anatomy changes over the migraine cycle, with specific anatomical changes occurring in the 24 hours prior to onset. These changes may contribute to the activation of the ascending trigeminal pathway by either an increase in basal traffic or by sensitising the trigeminal nuclei to external triggers, with activation ultimately resulting in perception of head pain during a migraine attack.

Significance Statement: It has been hypothesized that modulation of brainstem pain pathways may be critical for the initiation of migraine attacks. There is some evidence that altered brainstem function, possibly involving increased astrocyte activation, occurs immediately prior to a migraine attack. We sought to obtain evidence to support this theory. Using diffusion tensor imaging, we found that immediately prior to a migraine, mean diffusivity decreased in the spinal trigeminal nucleus, dorsomedial/dorsolateral pons, and midbrain periaqueductal gray matter/nucleus cuneiform. Mean diffusivity then increased again immediately following the migraine attack. Decreased mean diffusivity before a migraine is consistent with increased astrocyte activation, since astrocyte processes enlarge during activation. These changes may underlie changes in brainstem function that are essential for the generation of a migraine.

Opening of ATP-sensitive potassium channels causes migraine attacks: a new target for the treatment of migraine.

Al-Karagholi MA[1], Hansen JM[1], Guo S[1], Olesen J[1,2] , Ashina M[1].

Brain. **2019 Jul 10**. pii: awz199. doi: 10.1093/brain/awz199. PMID: 31292608. [Epub ahead of print]

Migraine is one of the most disabling and prevalent of all disorders. To improve understanding of migraine mechanisms and to suggest a new therapeutic target, we investigated whether opening of ATP-sensitive potassium channels (KATP) would cause migraine attacks. In this randomized, double-blind, placebo-controlled, crossover study, 16 patients aged 18-49 years with one to five migraine attacks a month were randomly allocated to receive an infusion of 0.05 mg/min KATP channel opener levcromakalim and placebo on two different days (ClinicalTrials.gov number, NCT03228355). The primary endpoints were the difference in incidence of migraine attacks, headaches and the difference in area under the curve (AUC) for headache intensity scores (0-12 h) and for middle cerebral artery blood flow velocity (0-2 h) between levcromakalim and placebo. Between 24 May 2017 and 23 November 2017, 16 patients randomly received levcromakalim and placebo on two different days. Sixteen patients (100%) developed migraine attacks after levcromakalim compared with one patient (6%) after placebo (P = 0.0001); the difference of incidence is 94% [95% confidence interval (CI) 78-100%]. The incidence of headache over the 12 h observation period was higher but not significant after levcromakalim (n = 16) than after placebo (n = 7) (P = 0.016) (95% CI 16-71%). The AUC for headache intensity was significantly larger after levcromakalim compared to placebo (AUC0-12h, P < 0.0001). There was no change in mean middle cerebral artery blood flow velocity after levcromakalim compared to placebo (AUC0-2hP = 0.46). Opening of KATP channels caused migraine attacks in all patients. This suggests a crucial role of these channels in migraine pathophysiology and that KATP channel blockers could be potential targets for novel drugs for migraine.

HEADACHE and MIGRAINE (Continued)

Trial of Galcanezumab in Prevention of Episodic Cluster Headache.

Goadsby PJ[1], Dodick DW[1], Leone M[1], Bardos JN[1], Oakes TM[1], Millen BA[1], Zhou C[1], Dowsett SA[1], Aurora SK[1], Ahn AH[1], Yang JY[1], Conley RR[1], Martinez JM[1].

N Engl J Med. **2019 Jul 11**;381(2):132-141. doi: 10.1056/NEJMoa1813440. PMID: 31291515.

BACKGROUND: Episodic cluster headache is a disabling neurologic disorder that is characterized by daily headache attacks that occur over periods of weeks or months. Galcanezumab, a humanized monoclonal antibody to calcitonin gene-related peptide, may be a preventive treatment for cluster headache.

METHODS: We enrolled patients who had at least one attack every other day, at least four total attacks, and no more than eight attacks per day during a baseline assessment, as well as a history of cluster headache periods lasting at least 6 weeks, and randomly assigned them to receive galcanezumab (at a dose of 300 mg) or placebo, administered subcutaneously at baseline and at 1 month. The primary end point was the mean change from baseline in the weekly frequency of cluster headache attacks across weeks 1 through 3 after receipt of the first dose. The key secondary end point was the percentage of patients who had a reduction from baseline of at least 50% in the weekly frequency of cluster headache attacks at week 3. Safety was also assessed.

RESULTS: Recruitment was halted before the trial reached the planned sample size of 162 because too few volunteers met the eligibility criteria. Of 106 enrolled patients, 49 were randomly assigned to receive galcanezumab and 57 to receive placebo. The mean (±SD) number of cluster headache attacks per week in the baseline period was 17.8±10.1 in the galcanezumab group and 17.3±10.1 in the placebo group. The mean reduction in the weekly frequency of cluster headache attacks across weeks 1 through 3 was 8.7 attacks in the galcanezumab group, as compared with 5.2 in the placebo group (difference, 3.5 attacks per week; 95% confidence interval, 0.2 to 6.7; P = 0.04). The percentage of patients who had a reduction of at least 50% in headache frequency at week 3 was 71% in the galcanezumab group and 53% in the placebo group. There were no substantial between-group differences in the incidence of adverse events, except that 8% of the patients in the galcanezumab group had injection-site pain.

CONCLUSIONS: Galcanezumab administered subcutaneously at a dose of 300 mg once monthly reduced the weekly frequency of attacks of episodic cluster headache across weeks 1 through 3 after the initial injection, as compared with placebo. (Funded by Eli Lilly; ClinicalTrials.gov number, NCT02397473.)

CHRONIC PAIN

A mind-body program for pain and stress management in active duty service members and veterans.

Millegan J[1], Denninger JW[2], Bui E[2], Jakubovic RJ[2], Ram V[1], Bhakta J[1], Hiller Lauby MD[3], Mehta DH[4], Sager JC[5], Fricchione G[2], Sylvia LG[2].

Psychol Serv. **2019 Jul 8**. doi: 10.1037/ser0000376. PMID: 31282706. [Epub ahead of print]

The Mind-Body Medicine (MBM) program at the Naval Medical Center San Diego, created in collaboration with the Benson-Henry Institute for Mind Body Medicine and the Home Base Program at Massachusetts General Hospital, is a 7-week program designed to facilitate stress management habits into patient treatment plans. The aim of this study is to test the feasibility and acceptability of a mind-body program for service members and veterans. Participants (N = 239) were primarily active duty service members of the U.S. Navy and Marine Corps reporting significant perceived stress (Stress Resiliency (SR) group; n = 124), or meeting criteria for chronic pain (Pain Management (PM) group; n = 115). Participants completed measures at preprogram and post-program assessing for perceived stress, pain, functional impairment, quality of life, and psychological and somatic symptoms. Changes in self-reported psychological symptoms and knowledge and practice of mind-body principles were examined. Participants across groups had significant improvement in most outcomes (perceived stress, response to stressful experience, functional impairment, sleep disturbance, depression, PTSD, and anxiety symptoms; and each quality of life domain aside from social relationships), with p values < .0017 (Bonferroni corrected level of significance). The SR group demonstrated significant improvements in primary outcomes of perceived stress and response to stressful experience, and the PM group demonstrated significant improvement in pain severity, but not perceived stress. Significant change was observed in knowledge and practice of mind-body medicine principles, and high satisfaction was reported. Results suggest that a mind-body program may improve physical and psychological functioning for service members, including those facing significant perceived stress and chronic pain.

CHRONIC PAIN (Continued)

Robot-Guided Neuronavigated Repetitive Transcranial Magnetic Stimulation (rTMS) in Central Neuropathic Pain.

Quesada C[1], Pommier B[2], Fauchon C[3], Bradley C[4], Créac'h C[5], Vassal F[2], Peyron R[5].

Arch Phys Med Rehabil. 2018 Nov;99(11):2203-2215.e1. doi: 10.1016/j.apmr.2018.04.013. PMID: 29750900. Epub **2018 May 9**.

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

OBJECTIVES: To confirm and extend previous results involving repetitive transcranial magnetic stimulation (rTMS) aimed at alleviating refractory central neuropathic pain (CNP). To evaluate pain relief in detail and to assess ongoing benefits after one year of treatment.

DESIGN: Prospective observational study.

SETTING: University hospital. Outpatient settings.

PARTICIPANTS: Patients (N=80) with chronic central pain after brain or spinal cord injuries.

INTERVENTIONS: High-frequency (20Hz) neuronavigated-rTMS sessions were applied on the primary motor cortex using a figure-of-eight coil positioned by a robotized arm. Patients received a minimum of 4 consecutive sessions, each separated by 3-4 weeks.

MAIN OUTCOME MEASURES: Percentage of pain relief (%R), duration of pain relief (DPR), numeric rating scale (NRS), neuropathic pain symptom inventory (NPSI), and pain relief score (PRS).

RESULTS: Seventy-one patients completed the study. On average, after the first 4 sessions, %R was 28% and DPR was 11 days. Fifty-four patients (76%) were responders with a permissive threshold of ≥10%R and 61% (43 patients) with a stringent threshold ≥30%R. After 12 months of treatment (15 sessions) we observed a cumulative effect on %R (48%), DPR (20d), and on the prevailing NPSI sub-score (-28%). This effect reached significance after 4 sessions and was further maintained over 12 months. Across participants, more than 1000 rTMS sessions were delivered over 6 years without any adverse effect.

CONCLUSION: These results confirm that multiple rTMS sessions are both safe and have potential as a treatment for CNP. An ongoing randomized controlled trial will allow teasing out of this effect from placebo analgesia.

Non-specific Low Back Pain: Inflammatory Profiles of Patients with Acute and Chronic Pain.

Teodorczyk-Injeyan JA[1], Triano JJ[1], Injeyan HS[2].

Clin J Pain. **2019 Jul 5**. doi: 10.1097/AJP.0000000000000745. PMID: 31283548. [Epub ahead of print]

BACKGROUND: The pathogenesis of low back pain (LBP) remains unclear. However, recent studies suggest that the inflammatory response may be inherent in spinal pain.

PURPOSE: To discern inflammatory profiles in patients with non-specific acute and chronic low back pain (LBP) in relation to those in asymptomatic subjects.

METHODS: Peripheral blood samples were obtained from asymptomatic subjects and patients with non-specific acute and chronic LBP reporting a minimum pain score of 3 on a 10-point visual analogue scale (VAS). The levels of in vitro production of pro-inflammatory (TNFα, IL-1β, IL-6, IL-2, IFN[Latin Small Letter Gamma]) and anti-inflammatory (IL-1 RA, sTNFR2 and IL-10) mediators were determined by specific immunoassays.

RESULTS: The mean VAS scores were comparable between the acute and chronic LBP patient groups. Compared to asymptomatic subjects, the production of TNFα, IL-1β, IL-6 and their ratios to IL-10 levels were significantly elevated in both patient groups (P=0.0001-0.003). In acute LBP group, the ratio of IL-2: IL-10 was also significantly increased (P=0.02). In contrast, the production of IFN[Latin Small Letter Gamma] was significantly reduced compared with the other study groups (P=0.005-0.01), nevertheless, it was positively correlated (P=0.006) with pain scores. In chronic LBP patients, the production of TNFα, IL-1RA and sTNFR2 was significantly increased (P=0.001-0.03) in comparison with the control and acute LBP groups, and TNFα and IL-1β levels were positively correlated (P<0.001) with VAS scores.

CONCLUSION: The inflammatory profiles of patients with acute and chronic LBP are distinct. Nonetheless, in both patient groups, an imbalance between pro- and anti-inflammatory mediator levels favors the production of pro-inflammatory components.

CHRONIC PAIN (Continued)

The search for pain biomarkers in the human brain.

Mouraux A[1], Iannetti GD[2,3].

Brain. **2018 Dec 1**;141(12):3290-3307. doi: 10.1093/brain/awy281. PMCID: PMC6262221. PMID: 30462175.

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

Non-invasive functional brain imaging is used more than ever to investigate pain in health and disease, with the prospect of finding new means to alleviate pain and improve patient wellbeing. The observation that several brain areas are activated by transient painful stimuli, and that the magnitude of this activity is often graded with pain intensity, has prompted researchers to extract features of brain activity that could serve as biomarkers to measure pain objectively. However, most of the brain responses observed when pain is present can also be observed when pain is absent. For example, similar brain responses can be elicited by salient but non-painful auditory, tactile and visual stimuli, and such responses can even be recorded in patients with congenital analgesia. Thus, as argued in this review, there is still disagreement on the degree to which current measures of brain activity exactly relate to pain. Furthermore, whether more recent analysis techniques can be used to identify distributed patterns of brain activity specific for pain can be only warranted using carefully designed control conditions. On a more general level, the clinical utility of current pain biomarkers derived from human functional neuroimaging appears to be overstated, and evidence for their efficacy in real-life clinical conditions is scarce. Rather than searching for biomarkers of pain perception, several researchers are developing biomarkers to achieve mechanism-based stratification of pain conditions, predict response to medication and offer personalized treatments. Initial results with promising clinical perspectives need to be further tested for replicability and generalizability.

IRRITABLE BOWEL SYNDROME

Serum Levels of Chemerin, Apelin, and Adiponectin in Relation to Clinical Symptoms, Quality of Life, and Psychological Factors in Irritable Bowel Syndrome.

Baram MA[1], Abbasnezhad A[1], Ghanadi K[2], Anbari K[3], Choghakhori R[1,4], Ahmadvand H[4,5].

J Clin Gastroenterol. **2019 Jul 12**. doi: 10.1097/MCG.0000000000001227. PMID: 31306342. [Epub ahead of print]

BACKGROUND: Adipokines have endocrine roles in metabolism and immunity. Dysregulation of adipokine levels is associated with several diseases with chronic inflammation. We aimed to assess the serum concentrations of chemerin, apelin, and adiponectin in irritable bowel syndrome (IBS). Furthermore, we evaluated the possible association of these adipokines with clinical symptoms, quality of life (QoL), and psychological factors.

MATERIALS AND METHODS: In this case-control study, 114 male and female IBS patients were recruited from outpatient clinics. Along with the IBS patients, 114 sex and age-matched healthy volunteers were recruited. Patients filled in the questionnaires of the IBS severity scoring system (IBSSS), gastrointestinal (GI) and somatic symptoms, IBS specific QoL (IBS-QoL), and psychological disorders, and went to the lab for blood sampling.

RESULTS: Serum levels of both adiponectin and apelin were significantly (P=0.04, 0.03, respectively) lower, whereas chemerin was significantly (P=0.01) higher in IBS patients. Chemerin was higher in IBS-D compared with both IBS-C and IBS-A, while apelin and adiponectin were not different between subtypes. After adjustments for confounders only, chemerin had a positive association with IB severity scoring system and GI symptoms. Furthermore, chemerin had positive associations, whereas apelin and adiponectin had inverse associations with somatic symptoms and psychological factors. There were no significant associations between adipokines including chemerin, apelin, and adiponectin, and IBS-QoL.

CONCLUSIONS: Chemerin had significant associations with both the severity of clinical symptoms and psychological factors in IBS; thus, it could be considered as a potential therapeutic target in these patients; however, further studies are needed.

IRRITABLE BOWEL SYNDROME (Continued)

Are There Potential Applications of Fecal Microbiota Transplantation beyond Intestinal Disorders?

Zhou Y[1,2], Xu H[1,2], Huang H[1,2], Li Y[1,2], Chen H[1,2], He J[1,2], Du Y[1,2], Chen Y[3], Zhou Y[1,2], Nie Y[1,2].

Biomed Res Int. **2019 Jul 29**;2019:3469754. doi: 10.1155/2019/3469754. PMCID: PMC6699279. eCollection 2019.

Intestinal microbial dysbiosis is associated with various intestinal and extraintestinal disorders. Fecal microbiota transplantation (FMT), a type of fecal bacteriotherapy, is considered an effective therapeutic option for recurrent *Clostridium difficile* infection (rCDI) and also has important value in other intestinal diseases including irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). The purpose of this review is to discuss promising therapeutic value in extraintestinal diseases associated with gut microbial dysbiosis, including liver, metabolic, chronic kidney, neuropsychiatric, allergic, autoimmune, and hematological diseases as well as tumors.

OTHER RESEARCH OF INTEREST

Targeting the PAC1 Receptor for Neurological and Metabolic Disorders.

Liao C[1], de Molliens MP[2], Schneebeli ST[1], Brewer M[1], Song G[3], Chatenet D[2], Braas KM[4], May V[4], Li J[5].

Curr Top Med Chem. **2019 Jul 8**. doi: 10.2174/1568026619666190709092647. PMID: 31284862. [Epub ahead of print]

The pituitary adenylate cyclase-activating polypeptide (PACAP)-selective PAC1 receptor (PAC1R, ADCYAP1R1) is a member of the vasoactive intestinal peptide (VIP)/secretin/glucagon family of G protein-coupled receptors (GPCRs). PAC1R has been shown to play crucial roles in the central and peripheral nervous systems. The activation of PAC1R initiates diverse downstream signal transduction pathways, including adenylyl cyclase, phospholipase C, MEK/ERK and Akt pathways that regulate a number of physiological systems to maintain functional homeostasis. Accordingly, at times of tissue injury or insult, PACAP/PAC1R activation of these pathways can be trophic to blunt or delay apoptotic events and enhance cell survival. Enhancing PAC1R signaling under these conditions has the potential to mitigate cellular damages associated with cerebrovascular trauma (including stroke), neurodegeneration (such as Parkinson's and Alzheimer's disease) or peripheral organ insults. Conversely, maladaptive PACAP/PAC1R signaling has been implicated in\ a number of disorders, including stress-related psychopathologies (i.e., depression, posttraumatic stress disorder, and related abnormalities), chronic pain and migraine, and metabolic diseases; abrogating PAC1R signaling under these pathological conditions represent opportunities for therapeutic intervention. Given the diverse PAC1R-mediated biological activities, the receptor has emerged as a relevant pharmaceutical target. In this review, we first describe the current knowledge regarding the molecular structure, dynamics, and function of PAC1R. Then, we discuss the roles of PACAP and PAC1R in the activation of a variety of signaling cascades related to the physiology and diseases of the nervous system. Lastly, we examine current drug design and development of peptides and small molecules targeting PAC1R based on a number of structure-activity relationship studies and key pharmacophore elements. At present, the rational design of PAC1R-selective peptide or small-molecule therapeutics is largely hindered by the lack of structural information regarding PAC1R activation mechanisms, the PACAP-PAC1R interface, and the core segments involved in receptor activation. Understanding the molecular basis governing the PACAP interactions with its different cognate receptors will undoubtedly provide a basis for the development and/or refinement of receptor-selective therapeutics.

OTHER RESEARCH OF INTEREST (Continued)

The Complex Interplay Between Weight, Chronic Pain, and Mood: How Team-Based Care and Personalized Approaches Can Improve Function and Quality of Life.

Geyer C[1].

Am J Lifestyle Med. 2019 Apr 23;13(4):362-366. doi: 10.1177/1559827619840638. PMCID: PMC6600612. PMID: 31285718. eCollection **2019 Jul-Aug**. [Note: Delayed posting in PubMed—Not previously listed in RAC Research Alerts.]

Patients presenting with a desire to lose weight often have underlying factors that complicate recommendations regarding diet and exercise. In this woman's story, a significant physical injury resulted in chronic pain and a loss in her ability to participate in activities she had previously enjoyed and which played a role in her self-identity. While her previous history of a mood disorder may have increased her risk of developing chronic pain, the impact her injury had on her sense of self was also a likely factor. A multidisciplinary approach that addressed her sense of loss; incorporated innovative adaptations that enabled her to exercise outdoors and led to a renewed sense of hope; helped her find creative outlets and increase her sense of self efficacy; and improve the quality of sleep was instrumental in supporting her ability to incorporate dietary change, lose weight, and improve her mood and well-being. The biopsychosocial model of pain provides a framework of understanding for the complex interplay between mood, pain, and social support, which in turn can impact weight and ability to incorporate lifestyle change. Addressing these underlying factors is a critical part of whole person health.

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