GULF WAR ILLNESS

Perspective: Scientific and ethical concerns pertaining to animal models of autoimmune/ autoinflammatory syndrome induced by adjuvants (ASIA).

Ameratunga R[1], Langguth D[2], Hawkes D[3].

Autoimmun Rev. **2018 Mar 8**. pii: S1568-9972(18)30045-4. doi: 10.1016/j.autrev.2017.11.033. PMID: 29526635. [Epub ahead of print]

The autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA) was first described in 2011. The aluminium containing adjuvants of vaccines were stated to be one of the main causes of the condition. Other disorders associated with ASIA include siliconosis, Gulf war syndrome, sick building syndrome and the macrophagic myositis syndrome. We have recently reviewed ASIA as defined by its authors. We have shown that the definition of ASIA is imprecise and includes all patients with an autoimmune disorder as well as potentially the entire population. Application of the Bradford Hill criteria for causality does not support ASIA as an outcome of exposure to aluminium containing adjuvants in vaccines. The advocates of ASIA highlight animal models as evidence for the existence of the disorder. However, as this review will demonstrate, animal models purporting to support the existence of ASIA have methodological, analytical and ethical flaws which, in our view refute the existence of the condition. Three publications by the advocates of ASIA were recently retracted from peer-reviewed journals. We call for a moratorium on animal experiments of ASIA until an independent inquiry has been conducted to determine the existence of a clinically relevant syndrome, identifiable as ASIA in humans.

The value of Autoimmune Syndrome Induced by Adjuvant (ASIA) - Shedding light on orphan diseases in autoimmunity.

Segal Y[1], Dahan S[2], Sharif K[3], Bragazzi NL[4], Watad A[3], Amital H[3].

Autoimmun Rev. **2018 Mar 8**. pii: S1568-9972(18)30057-0. doi: 10.1016/j.autrev.2017.11.037. PMID: 29526630. [Epub ahead of print]

Autoimmune Syndrome Induced by Adjuvant (ASIA) is a definition aimed to describe the common etiological process at the root of five clinical entities sharing similar symptomatology: macrophagic myofasciitis syndrome (MMF), Gulf War Syndrome (GWS), sick building syndrome (SBS), siliconosis, and post vaccination autoimmune phenomena. ASIA illustrates the role of environmental immune stimulating agents, or adjuvants, in the instigation of complex autoimmune reactions among individuals bearing a genetic preponderance for autoimmunity. The value of ASIA lies first in the acknowledgment it provides for patients suffering from these as yet ill-defined medical conditions. Equally important is the spotlight it sheds for further research of these poorly understood conditions sharing a common pathogenesis. In this article we elaborate on the significance of ASIA, review the current evidence in support of the syndrome, and address recent reservations raised regarding its validity.

Anxiety, neuroinflammation, cholinergic and GABAergic abnormalities are early markers of Gulf War illness in a mouse model of the disease.

Carreras I[1], Aytan N[2], Mellott T[3], Choi JK[4], Lehar M[5], Crabtree L[6], Leite-Morris K[7], Jenkins BG[8], Blusztajn JK[9], Dedeoglu A[10].

Brain Res. **2018 Feb 15**;1681:34-43. doi: 10.1016/j.brainres.2017.12.030. PMID: 29277710. Epub 2017 Dec 24.
[Abstract of this article listed in RAC Research Alerts for Jan. 02, 2018.]

Erratum in: Corrigendum to "Anxiety, neuroinflammation, cholinergic and GABAergic abnormalities are early markers of Gulf War illness in a mouse model of the disease" [Brain Res. 1681 (2018) 34-43]. [Brain Res. 2018]
[Correction of Figs. 1 and 3 not shown in their entirety in the original article.]

Gulf War Illness (GWI) is a chronic disease that affects the 1991 Gulf War (GW) veterans for which treatment is lacking. It has been hypothesized that drugs used to protect military personnel from chemical attacks and insects during the war: pyridostigmine bromide (PB),N, N-diethyl-m-toluamide (DEET), and permethrin (PER) together with stress may have contributed collectively and synergistically to generate GWI. There is a need to find markers of pathology to be used in pre-clinical trials. For this purpose we employed a previously validated mouse model of GWI evoked by daily exposure to PB (1.3 mg/kg), DEET (40 mg/kg), PER (0.13 mg/kg), and 5 min of restraint stress for 28 days to analyze behavior, brain pathology and neurochemical outcomes three months later. GWI-model mice were characterized by increased anxiety, decreased hippocampal levels of N-acetyl aspartate, GABA, the GABA-producing enzyme GAD-67 and microglial activation. We also observed that GWI model was sexually dimorphic on some measures: males had increased while females had decreased protein levels of the acetylcholine-synthesizing enzyme, choline acetyltransferase, in the septum and hippocampus and decreased levels of the receptor for brain-derived neurotrophic factor, TrkB140, in the hippocampus. Increased hippocampal levels of nerve growth factor were detected in males only. Together the data show behavioral and neuropathological abnormalities detected at 3 months post-exposure and that some of them are sexually dimorphic. Future preclinical studies for GWI may take advantage of this short latency model and should include both males and females as their response to treatment may differ.

CHRONIC FATIGUE SYNDROME

Immunoadsorption to remove ß2 adrenergic receptor antibodies in Chronic Fatigue Syndrome CFS/ME.

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PLoS One. **2018 Mar 15**;13(3):e0193672. doi: 10.1371/journal.pone.0193672. PMID: 29543914. eCollection 2018.

INTRODUCTION: Infection-triggered disease onset, chronic immune activation and autonomic dysregulation in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) point to an autoimmune disease directed against neurotransmitter receptors. We had observed elevated autoantibodies against ß2 adrenergic receptors, and muscarinic 3 and 4 acetylcholine receptors in a subset of patients. Immunoadsorption (IA) was shown to be effective in removing autoantibodies and improve outcome in various autoimmune diseases.

METHODS: 10 patients with post-infectious CFS/ME and elevated ß2 autoantibodies were treated with IA with an IgG-binding column for 5 days. We assessed severity of symptoms as outcome parameter by disease specific scores. Antibodies were determined by ELISA and B cell phenotype by flow cytometry.

RESULTS: IgG levels dropped to median 0.73 g/l (normal 7-16 g/l) after the 4th cycle of IA, while IgA and IgM levels remained unchanged. Similarly, elevated ß2 IgG antibodies rapidly decreased during IA in 9 of 10 patients. Also 6 months later ß2 autoantibodies were significantly lower compared to pretreatment. Frequency of memory B cells significantly decreased and frequency of plasma cells increased after the 4th IA cycle. A rapid improvement of symptoms was reported by 7 patients during the IA. 3 of these patients had long lasting moderate to marked improvement for 6-12+ months, 2 patients had short improvement only and 2 patients improved for several months following initial worsening.

CONCLUSIONS: IA can remove autoantibodies against ß2 adrenergic receptor and lead to clinical improvement. B cell phenotyping provides evidence for an effect of IA on memory B cell development. Data from our pilot trial warrants further studies in CFS/ME.

Functional Status and Well-Being in People with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Compared with People with Multiple Sclerosis and Healthy Controls.

Kingdon CC[1], Bowman EW[2], Curran H[2], Nacul L[2], Lacerda EM[2].

Pharmacoecon Open. **2018 Mar 13**. doi: 10.1007/s41669-018-0071-6. PMID: 29536371. [Epub ahead of print]

BACKGROUND: People with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) continue to struggle to have their condition recognised as disabling in the face of public and professional prejudice and discrimination.

OBJECTIVE: The aim of this study was to compare the functional status and well-being of people with well-characterised ME/CFS with people with multiple sclerosis (PWMS), as well as healthy controls (HCs).

METHODS: In this cross-sectional study, we used data collected as part of the UK ME/CFS Biobank to compare actual participant scores from the Medical Outcomes Survey Short Form-36 v2™ (SF-36v2™) between groups, as a proxy for impact of disability, and from a bespoke questionnaire seeking data on employment and income.

RESULTS: People with ME/CFS scored significantly lower than PWMS or HCs in almost all SF-36v2™ areas. Prominent were lower scores for people with ME/CFS in the Physical Component Summary and Role Physical and Social Function domains, while the smallest differences were seen in the Mental Health domain. Responses to the bespoke questionnaire indicated that people with ME/CFS in this study work fewer hours and have lower incomes compared with people in the other two groups.

CONCLUSIONS: Using SF-36v2™ scores as a proxy, people with ME/CFS were measurably more disabled than PWMS or HCs in this study population. Furthermore, employment and income data are consistent with loss of functional status. These findings should encourage the health community to recognise the disabling effects of ME/CFS, to advocate for the needs of people with ME/CFS, and to investigate strategies to address the cost of the disease to both individuals and society.

HEADACHE and MIGRAINE

CaMKII-dependent endoplasmic reticulum fission by whisker stimulation and during cortical spreading depolarization.

Kucharz K[1], Lauritzen M[1,2].

Brain. **2018 Mar 12**. doi: 10.1093/brain/awy036. PMID: 29538620. [Epub ahead of print]

Cortical spreading depolarization waves, the cause underlying migraine aura, are also the markers and mechanism of pathology in the acutely injured human brain. Propagation of spreading depolarization wave uniquely depends on the interaction between presynaptic and postsynaptic glutamate N-methyl-d-aspartate receptors (NMDARs). In the normally perfused brain, even a single wave causes a massive depolarization of neurons and glia, which results in transient loss of neuronal function and depression of the ongoing electrocorticographic activity. Endoplasmic reticulum is the cellular organelle of particular importance for modulation of neurotransmission. Neuronal endoplasmic reticulum structure is assumed to be persistently continuous in neurons, but is rapidly lost within 1 to 2 min of global cerebral ischaemia, i.e. the organelle disintegrates by fission. This phenomenon appears to be timed with the cardiac arrest-induced cortical spreading depolarizations, rather than ensuing cell death. To what extent NMDAR-dependent processes may trigger neuronal endoplasmic reticulum fission and whether fission is reversible in the normally perfused brain is unknown. We used two-photon microscopy to examine neuronal endoplasmic reticulum structural dynamics during whisker stimulation and cortical spreading depolarizations in vivo. Somatosensory stimulation triggered loss of endoplasmic reticulum continuity, a likely outcome of constriction and fission, in dendritic spines within less than 10 s of stimulation, which was spontaneously reversible and recovery to normal took 5 min. The endoplasmic reticulum fission was inhibited by blockade of NMDAR and Ca2+/calmodulin-dependent protein kinase II (CaMKII) activated downstream of the NMDARs, whereas inhibition of guanosine triphosphate hydrolases hindered regain of endoplasmic reticulum continuity, i.e. fusion. In contrast to somatosensory stimulation, endoplasmic reticulum fission during spreading depolarization was widespread and present in dendrites and spines, and was preceded by dramatic rise in intracellular Ca2+. The endoplasmic reticulum fission during spreading depolarization was more persistent, as 1 h after the depolarization cortical neurons still exhibited loss of endoplasmic reticulum continuity. Notably, endoplasmic reticulum fission was accompanied with loss of electrocorticographic activity, whereas subsequent regain of synaptic function paralleled the organelle fusion. Furthermore, blocking CaMKII activity partly rescued endoplasmic reticulum fission and markedly shortened the recovery time of brain spontaneous activity. Thus, prevention of endoplasmic reticulum fission with CaMKII inhibitors may be a novel strategy to rescue brain function in patients with migraine and a promising therapeutic avenue in the acutely injured brain.

Carbon monoxide inhalation induces headache but no migraine in patients with migraine without aura.

Ghanizada H[1], Arngrim N[1], Schytz HW[1], Olesen J[1], Ashina M[1].

Cephalalgia. **2018 Jan 1**:333102418765771. doi: 10.1177/0333102418765771. PMID: 29540069. [Epub ahead of print]

Introduction Carbon monoxide is an endogenously produced signaling gasotransmitter known to cause headache and vasodilation. We hypothesized that inhalation of carbon monoxide would induce migraine-like attacks in migraine without aura patients. Methods In a randomized, double-blind, placebo-controlled crossover design, 12 migraine patients were allocated to inhalation of carbon monoxide (carboxyhemoglobin 22%) or placebo on two separate days. Headache and migraine characteristics were recorded during hospital (0-2 hours) and post-hospital (2-13 hours) phases. Results Six patients (50%) developed migraine-like attacks after carbon monoxide compared to two after placebo (16.7%) ($p = 0.289$). The median time to onset of migraine-like attacks after carbon monoxide inhalation was 7.5 h (range 3-12) compared to 11.5 h (range 11-12) after placebo. Nine out of 12 patients (75%) developed prolonged headache after carbon monoxide. The area under the curve for headache score (0-13 hours) was increased after carbon monoxide compared with placebo ($p = 0.033$). Conclusion Carbon monoxide inhalation did not provoke more migraine-like attacks in migraine patients compared to placebo, but induced more headache in patients compared to placebo. These data suggest that non-toxic concentrations of carbon monoxide had low potency in migraine induction and that the carbon monoxide inhalation model is not suitable to study migraine.

HEADACHE and MIGRAINE (Continued)

Cluster Headache Clinical Phenotypes: Tobacco Nonexposed (Never Smoker and No Parental Secondary Smoke Exposure as a Child) versus Tobacco-Exposed: Results from the United States Cluster Headache Survey.

Rozen TD[1].

Headache. **2018 Mar 14**. doi: 10.1111/head.13295. PMID: 29536529. [Epub ahead of print]

OBJECTIVE: To present results from the United States Cluster Headache Survey comparing the clinical presentation of tobacco nonexposed and tobacco-exposed cluster headache patients.

BACKGROUND: Cluster headache is uniquely tied to a personal history of tobacco usage/cigarette smoking and, if the individual cluster headache sufferer did not smoke, it has been shown that their parent(s) typically did and that individual had significant secondary smoke exposure as a child. The true nontobacco exposed (no personal or secondary exposure) cluster headache sufferer has never been fully studied.

METHODS: The United States Cluster Headache Survey consisted of 187 multiple choice questions related to cluster headache including: patient demographics, clinical headache characteristics, family history, triggers, smoking history (personal and secondary), and headache-related disability. The survey was placed on a website from October through December 2008.

RESULTS: One thousand one hundred thirty-four individuals completed the survey. One hundred thirty-three subjects or 12% of the surveyed population had no personal smoking/tobacco use history and no secondary smoke exposure as an infant/child, thus a nontobacco exposed population. In the nonexposed population, there were 87 males and 46 females with a gender ratio of 1.9:1. Episodic cluster headache occurred in 80% of nonexposed subjects. One thousand and one survey responders or 88% were tobacco-exposed (729 males and 272 females) with a gender ratio of 2.7:1. Eighty-three percent had a personal smoking history, while only 17% just had parents who smoked with secondary smoke exposure. Eighty-five percent of smokers had double exposure with a personal smoking history and secondary exposure as a child.

SIGNIFICANT HIGHLIGHTS FROM THE SURVEY: Nonexposed cluster headache subjects are significantly more likely to develop cluster headache at ages 40 years and younger, while the exposed sufferers are significantly more likely to develop cluster headache at 40 years of age and older. Nonexposed patients have a statistically significant higher frequency of a migraine family history. The exposed population is statistically significantly more likely to have a history of head trauma 19% vs the nonexposed population 10% (P = .02). Tobacco exposed are significantly more likely to transition from episodic to chronic cluster headache (23% vs 14%, P = .02). Cranial autonomic symptoms as well as agitation are more common in tobacco exposed. Nonexposed are less likely to have specific cluster headache triggers. Exposed are significantly more likely to be triggered by alcohol. Tobacco exposed are significantly heavier caffeine users than nonexposed. Nonexposed are significantly more likely to have cluster headache cycles that vary throughout the year than exposed (52% vs 40%, P = .02). Exposed are much more likely to develop cluster headache from 12 am to 6 am than non exposed. Exposed experience significantly more frequent attacks per day and longer duration cycles than nonexposed. A significantly larger percent of the exposed population (57%) has suicidal ideations with their syndrome than nonexposed (43%) (P = .003). In regard to disability, both subtypes are disabled by their headaches, but exposed have more work related disability and lost home-days from headache. Both subgroups have a poor overall response to preventive and abortive medication outside of inhaled oxygen and injectable sumatriptan.

CONCLUSION: Cluster headache sufferers who were never exposed to tobacco (personal or secondary as a child) appear to present uniquely compared to the tobacco exposed subgroup. The tobacco exposed clinical phenotype appears to have a more severe syndrome based on attack frequency, cycle duration, and headache related disability. Tobacco exposure is associated with cluster headache chronification. The nonexposed subtype appears to have an earlier age of onset, higher rate of familial migraine, and less circadian periodicity and daytime entrainment, suggesting a possible different underlying pathology than in the tobacco exposed sub-form.

CHRONIC PAIN

Prevalence of Pain Diagnoses and Burden of Pain Among Active Duty Soldiers, FY2012.

Reif S[1], Adams RS[1], Ritter GA[1], Williams TV[2,3], Larson MJ[1].

Mil Med. **2018 Mar 14**. doi: 10.1093/milmed/usx200. PMID: 29547946. [Epub ahead of print]

Introduction: Soldiers are at risk for acute and chronic pain due to the mental and physical challenges of military duties and ongoing training for force readiness. With the burden of pain on any individual attributable across pain sources, a broad perspective that goes beyond prior characterizations of pain is important. We aim to further the understanding of pain's effects among non-deployed active duty soldiers and the Military Health System (MHS), by describing prevalence of 10 painful conditions, reported pain levels, duration of pain and impact of pain on military duty limitations.

Methods: Data are from the MHS Data Repository including outpatient MHS direct care encounters, claims for outpatient purchased care from civilian providers, and vital records, for all soldiers continuously enrolled in TRICARE and not deployed in FY 2012. Ten pain-related diagnostic categories were conceptually derived for this analysis and identified using ICD-9-CM diagnostic codes. We report the FY 2012 prevalence at the soldier-level (N = 297,120) for each pain category as a primary diagnosis, as well as in any diagnostic position, and at the soldier-level for reported pain level, duration, and military duty limitations. Institutional Review Board approval was obtained prior to analyses.

Results: Overall, 63% of soldiers had at least one pain diagnosis and 59% had a primary pain diagnosis during FY 2012. Back and neck pain (22%), non-traumatic joint disorders (28%), and other musculoskeletal pain (30%) were the most frequent categories for primary diagnosis. Nearly two-thirds of soldiers had a primary pain diagnosis in more than one category, and 23% in four or more categories. Moderate or severe pain levels were reported at least once during the year by 55% of soldiers who had a primary pain diagnosis. In the subsample of soldiers with primary pain in the first quarter, duration and chronicity of pain diagnoses varied by pain category: the back and neck pain category was the most common for both persistent pain occurring in each quarter of FY 2012 (23%) and chronic pain lasting for at least 3 mo (62%). In most pain categories, the majority of soldiers were released without duty limitations.

Conclusion: These data provide a deeper understanding of pain diagnoses and burden of pain among active duty soldiers. A substantial proportion of soldiers with pain diagnoses were seen for pain self-reported as only mild, or that did not result in significant restrictions in military duty limitations. However, given the prevalence of multiple pain diagnoses and common reports of moderate or severe pain and long duration, complex interventions may be required to minimize the effect of pain on force readiness. This encounters-based analysis is likely an underestimate of presence of pain, and does not include contextual factors that could better describe the true effect of pain among this population.

Identification of the key genes associated with neuropathic pain.

Liu H[1], Xia T[1], Xu F[1], Ma Z[1], Gu X[1].

Mol Med Rep. **2018 Mar 9**. doi: 10.3892/mmr.2018.8718. PMID: 29532897. [Epub ahead of print]

Neuropathic pain is a chronic pain state associated with multiple etiologies that results in considerable social and economic burden. The identification of key genes associated with neuropathic pain is important for the development of novel therapies. Therefore, the present study downloaded the gene expression profile GSE15041 from the Gene Expression Omnibus database. The unverified gene chip was removed and the microarray data was normalized following quality control. The limma package in R was used to screen the differentially expressed genes (DEGs), followed by Gene Ontology and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. Furthermore, a protein-protein interaction (PPI) network based on the identified DEGs was constructed to select hub proteins, and reverse transcription-quantitative polymerase chain reaction was performed to detect the expression of these proteins in a mouse model of neuropathic pain. In total, 86 common DEGs were identified. DEGs were significantly enriched in 'extracellular space' and KEGG pathway enrichment analysis demonstrated that the DEGs were significantly enriched in inflammatory diseases and the mitogen-activated protein kinase signaling pathway. The PPI network consisted of 27 nodes (proteins) and 47 PPI edges (interactions). Interleukin (IL)-6, transcription factor AP-1 (c-Jun) and urikinase-type plasminogen activator (Plau) were identified as hub proteins and key genes in neuropathic pain. The mRNA expression of these hub proteins was significantly increased in the neuropathic pain model, compared with the sham group. IL-6, c-Jun, and Plau may be involved in development of neuropathic pain and further research investigating the exact role of these key genes is required.

CHRONIC PAIN (Continued)

Gender differences in functional connectivities between insular subdivisions and selective pain-related brain structures.

Dai YJ[1,2,3], Zhang X[1], Yang Y[1], Nan HY[1], Yu Y[1], Sun Q[1], Yan LF[1], Hu B[1], Zhang J[1], Qiu ZY[4], Gao Y[4], Cui GB[5], Chen BL[6], Wang W[7].

J Headache Pain. **2018 Mar 14**;19(1):24. doi: 10.1186/s10194-018-0849-z. PMID: 29541875.

BACKGROUND: The incidence of pain disorders in women is higher than in men, making gender differences in pain a research focus. The human insular cortex is an important brain hub structure for pain processing and is divided into several subdivisions, serving different functions in pain perception. Here we aimed to examine the gender differences of the functional connectivities (FCs) between the twelve insular subdivisions and selected pain-related brain structures in healthy adults.

METHODS: Twenty-six healthy males and 11 age-matched healthy females were recruited in this cross-sectional study. FCs between the 12 insular subdivisions (as 12 regions of interest (ROIs)) and the whole brain (ROI-whole brain level) or 64 selected pain-related brain regions (64 ROIs, ROI-ROI level) were measured between the males and females.

RESULTS: Significant gender differences in the FCs of the insular subdivisions were revealed: (1) The FCs between the dorsal dysgranular insula (dId) and other brain regions were significantly increased in males using two different techniques (ROI-whole brain and ROI-ROI analyses); (2) Based on the ROI-whole brain analysis, the FC increases in 4 FC-pairs were observed in males, including the left dId - the right median cingulate and paracingulate/ right posterior cingulate gyrus/ right precuneus, the left dId - the right median cingulate and paracingulate, the left dId - the left angular as well as the left dId - the left middle frontal gyrus; (3) According to the ROI-ROI analysis, increased FC between the left dId and the right rostral anterior cingulate cortex was investigated in males.

CONCLUSION: In summary, the gender differences in the FCs of the insular subdivisions with pain-related brain regions were revealed in the current study, offering neuroimaging evidence for gender differences in pain processing.

TRIAL REGISTRATION: ClinicalTrials.gov, NCT02820974 . Registered 28 June 2016.

Trends in Opioid Use and Prescribing in Medicare, 2006-2012.

Axeen S[1].

Health Serv Res. **2018 Mar 12**. doi: 10.1111/1475-6773.12846. PMID: 29532477. [Epub ahead of print]

OBJECTIVE: To determine characteristics and trends in opioid use, questionable use, and prescribing in Medicare.

STUDY SETTING: Opioid prescriptions filled through Medicare Part D for beneficiaries with full-year, fee-for-service Medicare coverage during 2006 to 2012.

STUDY DESIGN: Retrospective analysis of a 20 percent sample of Medicare claims data. Estimates are adjusted using multivariable regression analysis.

DATA COLLECTION: Opioid use, opioid abuse, questionable opioid use, and opioid prescribing by specialty.

PRINCIPAL FINDINGS: Opioid use in Medicare was stable from 2006 to 2012 on average. More than 1 in 3 beneficiaries filled an opioid prescription annually; about 1 in 10 were chronic opioid users. The distribution of opioid users shifted in favor of diagnoses often associated with chronic pain. Opioid users were increasingly likely to abuse opioids or display patterns of questionable use from 2006 to 2010, with a slowdown in later years. Average outcomes mask significant variation as the distribution of opioid use widened over the analysis period. Prescribing quantity and intensity varied by specialty. The largest quantity increases were among nurse practitioners and physician assistants.

CONCLUSIONS: Opioid utilization and prescribing are increasingly heterogeneous from 2006 to 2012. Future research should focus on explaining differential trends in utilization and prescribing.

CHRONIC PAIN (Continued)

Circuit dissection of the role of somatostatin in itch and pain.

Huang J[1,2], Polgár E[3], Solinski HJ[1], Mishra SK[1,4], Tseng PY[1], Iwagaki N[3], Boyle KA[3], Dickie AC[3], Kriegbaum MC[1], Wildner H[5], Zeilhofer HU[5], Watanabe M[6], Riddell JS[3], Todd AJ[7], Hoon MA[8].

Nat Neurosci. **2018 Mar 19**. doi: 10.1038/s41593-018-0119-z. [Epub ahead of print]

Stimuli that elicit itch are detected by sensory neurons that innervate the skin. This information is processed by the spinal cord; however, the way in which this occurs is still poorly understood. Here we investigated the neuronal pathways for itch neurotransmission, particularly the contribution of the neuropeptide somatostatin. We find that in the periphery, somatostatin is exclusively expressed in Nppb$^+$ neurons, and we demonstrate that Nppb$^+$somatostatin$^+$ cells function as pruriceptors. Employing chemogenetics, pharmacology and cell-specific ablation methods, we demonstrate that somatostatin potentiates itch by inhibiting inhibitory dynorphin neurons, which results in disinhibition of GRPR$^+$ neurons. Furthermore, elimination of somatostatin from primary afferents and/or from spinal interneurons demonstrates differential involvement of the peptide released from these sources in itch and pain. Our results define the neural circuit underlying somatostatin-induced itch and characterize a contrasting antinociceptive role for the peptide.

OTHER RESEARCH OF INTEREST

Implementing and Evaluating Genomic Screening Programs in Health Care Systems

Proceedings of a Workshop (2018): National Academies of Sciences, Engineering, and Medicine. 2018. *Implementing and Evaluating Genomic Screening Programs in Health Care Systems: Proceedings of a Workshop*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25048.

Contributors: National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Roundtable on Genomics and Precision Health; Siobhan Addie, Meredith Hackmann, Theresa Wizemann, and Sarah Beachy, Rapporteurs. Download PDF. Read Online

Genomic applications are being integrated into a broad range of clinical and research activities at health care systems across the United States. This trend can be attributed to a variety of factors, including the declining cost of genome sequencing and the potential for improving health outcomes and cutting the costs of care. The goals of these genomics-based programs may be to identify individuals with clinically actionable variants as a way of preventing disease, providing diagnoses for patients with rare diseases, and advancing research on genetic contributions to health and disease. Of particular interest are genomics- based screening programs, which will, in this publication, be clinical screening programs that examine genes or variants in unselected populations in order to identify individuals who are at an increased risk for a particular health concern (e.g., diseases, adverse drug outcomes) and who might benefit from clinical interventions. On November 1, 2017, the National Academies of Sciences, Engineering, and Medicine hosted a public workshop to explore the challenges and opportunities associated with integrating genomics-based screening programs into health care systems.

Midlife cardiovascular fitness and dementia: A 44-year longitudinal population study in women.

Hörder H[1], Johansson L[2], Guo X[2], Grimby G[2], Kern S[2], Östling S[2], Skoog I[2].

Neurology. **2018 Mar 14**. pii: 10.1212/WNL.0000000000005290. doi: PMID: 29540588. [Epub ahead of print]

OBJECTIVE: To investigate whether greater cardiovascular fitness in midlife is associated with decreased dementia risk in women followed up for 44 years.

METHODS: A population-based sample of 1,462 women 38 to 60 years of age was examined in 1968. Of these, a systematic subsample comprising 191 women completed a stepwise-increased maximal ergometer cycling test to evaluate cardiovascular fitness. Subsequent examinations of dementia incidence were done in 1974, 1980, 1992, 2000, 2005, and 2009. Dementia was diagnosed according to DSM-III-R criteria on the basis of information from neuropsychiatric examinations, informant interviews, hospital records, and registry data up to 2012. Cox regressions were performed with adjustment for socioeconomic, lifestyle, and medical confounders.

RESULTS: Compared with medium fitness, the adjusted hazard ratio for all-cause dementia during the 44-year follow-up was 0.12 (95% confidence interval [CI] 0.03-0.54) among those with high fitness and 1.41 (95% CI 0.72-2.79) among those with low fitness. High fitness delayed age at dementia onset by 9.5 years and time to dementia onset by 5 years compared to medium fitness.

CONCLUSIONS: Among Swedish women, a high cardiovascular fitness in midlife was associated with a decreased risk of subsequent dementia. Promotion of a high cardiovascular fitness may be included in strategies to mitigate or prevent dementia. Findings are not causal, and future research needs to focus on whether improved fitness could have positive effects on dementia risk and when during the life course a high cardiovascular fitness is most important.

OTHER RESEARCH OF INTEREST (Continued)

Behaviors, movements, and transmission of droplet-mediated respiratory diseases during transcontinental airline flights.

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Proc Natl Acad Sci U S A. **2018 Mar 19**. pii: 201711611. doi: 10.1073/pnas.1711611115. PMID: 29555754. [Epub ahead of print]

With over 3 billion airline passengers annually, the inflight transmission of infectious diseases is an important global health concern. Over a dozen cases of inflight transmission of serious infections have been documented, and air travel can serve as a conduit for the rapid spread of newly emerging infections and pandemics. Despite sensational media stories and anecdotes, the risks of transmission of respiratory viruses in an airplane cabin are unknown. Movements of passengers and crew may facilitate disease transmission. On 10 transcontinental US flights, we chronicled behaviors and movements of individuals in the economy cabin on single-aisle aircraft. We simulated transmission during flight based on these data. Our results indicate there is low probability of direct transmission to passengers not seated in close proximity to an infectious passenger. This data-driven, dynamic network transmission model of droplet-mediated respiratory disease is unique. To measure the true pathogen burden, our team collected 229 environmental samples during the flights. Although eight flights were during Influenza season, all qPCR assays for 18 common respiratory viruses were negative.

Altered expression of the Cdk5 activator-like protein, Cdk5α, causes neurodegeneration in part by accelerating the rate of aging.

Spurrier J[1,2], Shukla AK[1], McLinden K[3], Johnson K[1], Giniger E[4].

Dis Model Mech. **2018 Feb 21**. pii: dmm.031161. doi: 10.1242/dmm.031161. PMID: 29469033 [Epub ahead of print]

Aging is the greatest risk factor for neurodegeneration, but the connection between the two processes remains opaque. This is in part for want of a rigorous way to define physiological age, as opposed to chronological age. Here we develop a comprehensive metric for physiological age in *Drosophila,* based on genome-wide expression profiling. We applied this metric to a model of adult-onset neurodegeneration, increased or decreased expression of the activating subunit of the Cdk5 protein kinase, encoded by the gene *Cdk5α*, the ortholog of mammalian p35. *Cdk5α*-mediated degeneration was associated with a 27-150% acceleration of the intrinsic rate of aging, depending on the tissue and genetic manipulation. Gene ontology analysis and direct experimental tests revealed that affected, age-associated processes included numerous core phenotypes of neurodegeneration, including enhanced oxidative stress and impaired proteostasis. Taken together, our results suggest that *Cdk5α*-mediated neurodegeneration results from accelerated aging, in combination with cell-autonomous neuronal insults. These data fundamentally recast our picture of the relationship between neurodegeneration and its most prominent risk factor, natural aging.

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