At the Root of 3 "Long" Diseases: Persistent Antigens Inflicting Chronic Damage on the Brain and Other Organs in Gulf War Illness, Long-COVID-19, and Chronic Fatigue Syndrome

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Neuroscience Insights, 2022

Persistent Toxic Anthrax Vaccine Antigen in Gulf War Illness

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August 12, 2024

Persistent Antigens – Q & A

- Q1: What are “persistent antigens”?
- A1:Proteins (or protein fragments) that cannot be removed from the body

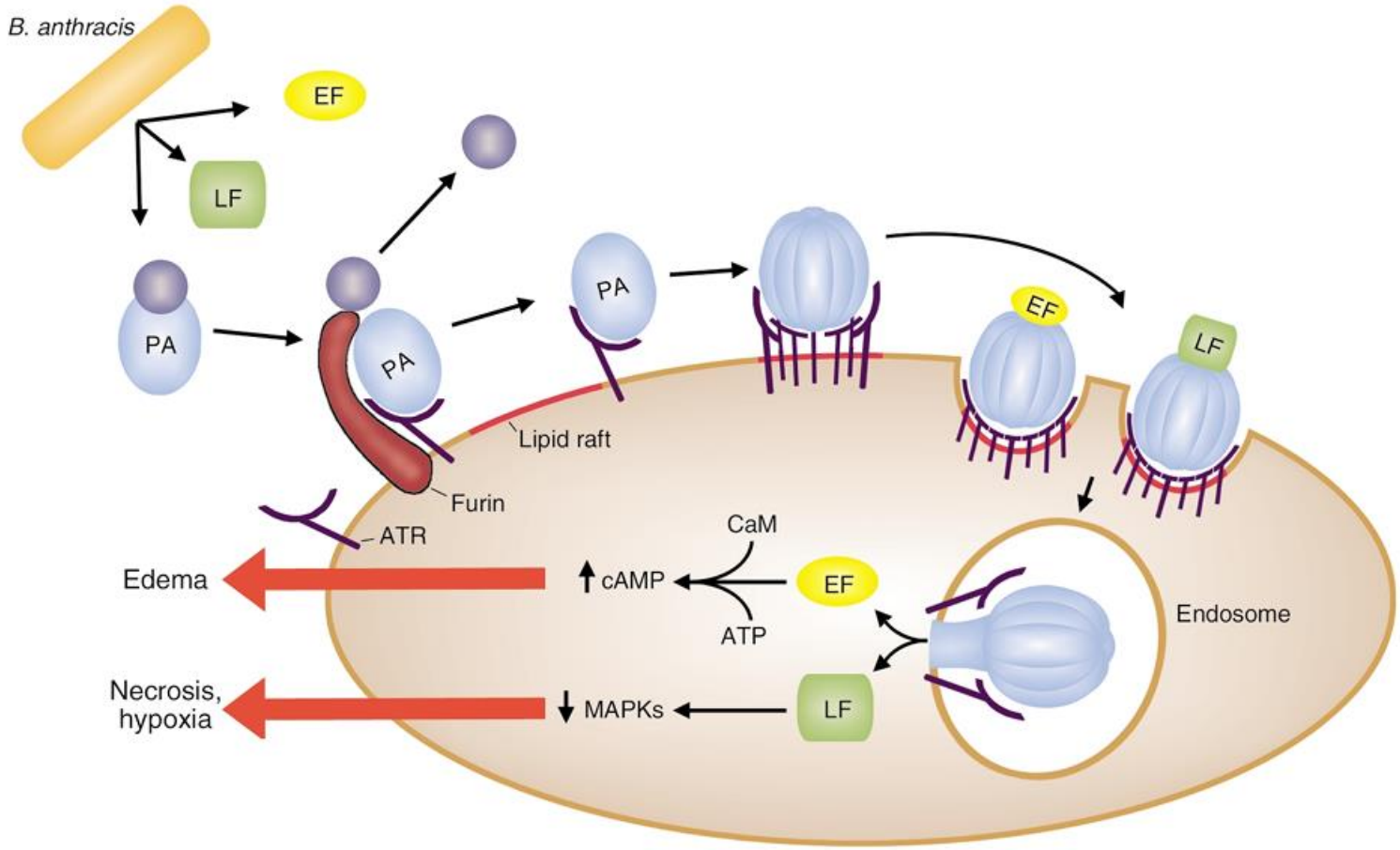
- Q2: Where do they come from?
- A2: Microorganisms (bacteria, viruses), following infection or vaccination

- Q3: Why they persist?
- A3: Because the immune system cannot get rid of them, for 2 main possible reasons (alone or in combination):
  - (a) The immune system is compromised (e.g. AIDS, immunosuppressive medications)
  - (b) Lack of suitable immunogenetic makeup (Human Leukocyte Antigen, HLA) to eliminate them by killing the cells that contain them (HLA Class I genes) and/or making antibodies against them (HLA Class II genes). Each individual carries 2 alleles of each of 3 classical HLA-I and HLA-II genes (A, B, C for HLA-I and DPB1, DQB1, DRB1 for HLA-II), for a total of 12 HLA alleles. The repertoire of proteins that can be eliminated is limited by the individual’s HLA set, hence the antigen persistence in the absence of suitable antigen-HLA match

Persistent Antigens → Pathogens

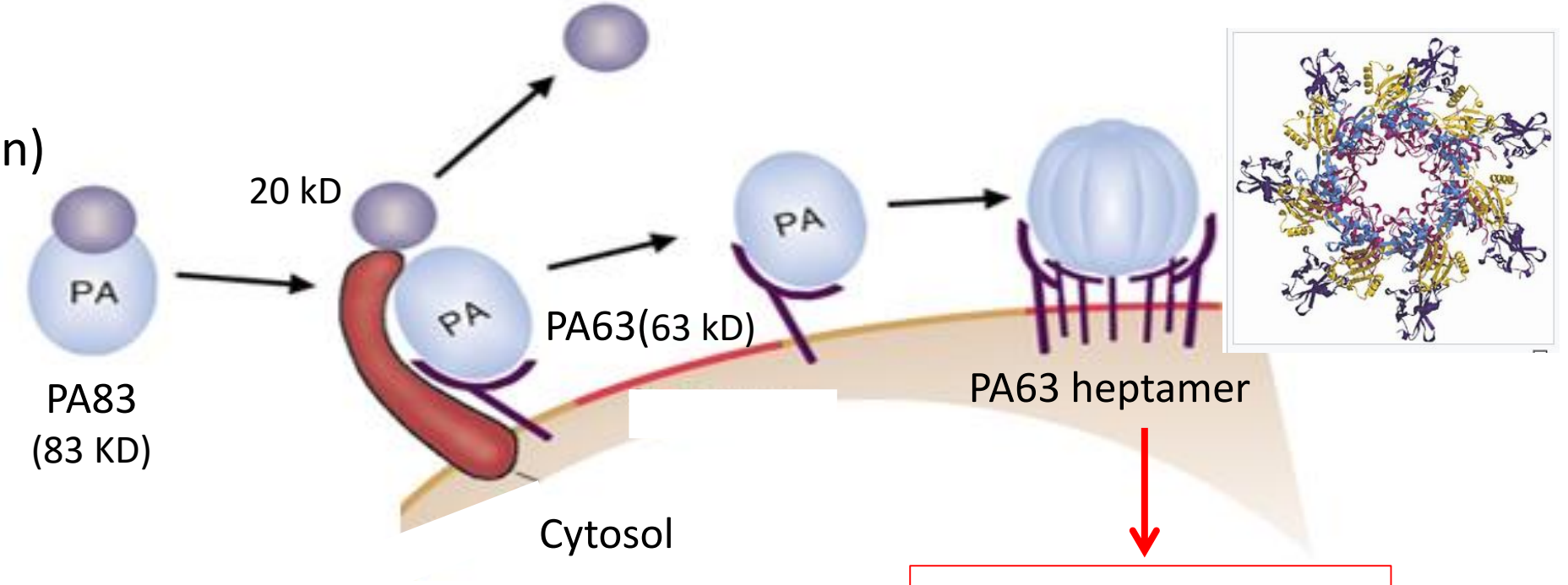
- Persistent antigens can cause harm by various mechanisms, alone or (frequently) in combination, by:
  - Inflicting direct cell damage → atrophy (anthrax protective antigen [PA], and others)
  - Disrupting cell structure and function (mitochondrial dysfunction → fatigue; most chronic disorders, e.g. GWI, chronic Lyme disease)
  - Inducing chronic inflammation (Peptidoglycan of *Borrelia burgdorferi* [Lyme disease], PA [GWI], and others)
  - Stimulating continuously the immune system → "immune fatigue" → vulnerability to infections (proteins of viruses: Human Immunodeficiency Virus [HIV], Epstein-Barr Virus [EBV – Human Herpes Virus 4], Cytomegalic Virus [CMV – Human Herpes Virus 5], other viruses [SARS-CoV-2? / Long COVID]
  - Inducing autoimmunity (molecular mimicry, or as a result of cell death and/or chronic inflammation)
  - Other mechanisms (to be identified) in:
    - SARS-CoV-2 / Long COVID
    - [Chronic Fatigue Syndrome]
    - [Chronic Multisymptom Illness (GWI+)]

ANTHRAX (Disease)



Price AS, Journal of Clinical Investigation, 2003

Anthrax Vaccine
(Protective Antigen)



Cell damage to:
Membrane permeability
Cytoskeleton integrity
Mitochondrial function

CELL DEATH

Atrophy
Inflammation
Autoimmunity

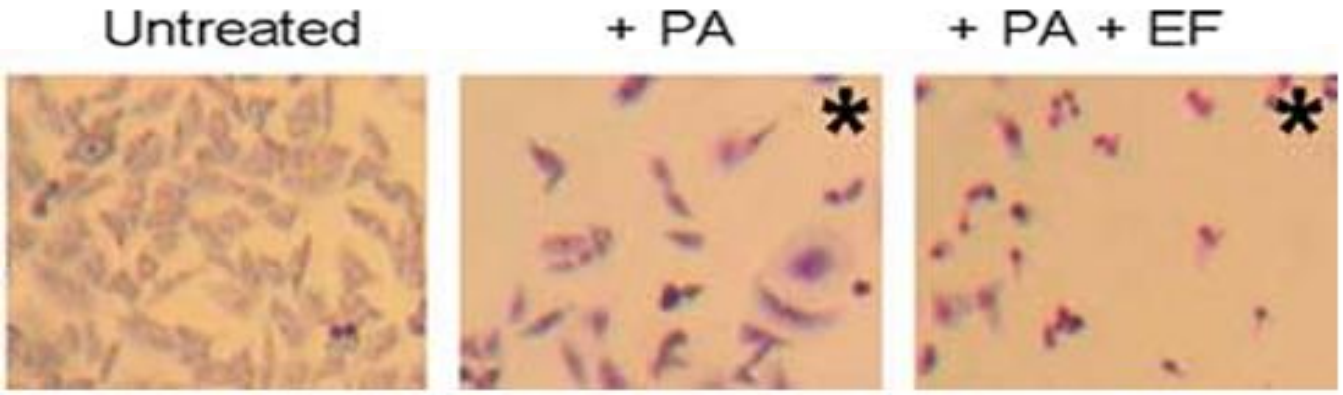
Toxicity of Anthrax Toxin Is Influenced by Receptor Expression

Sarah C. Taft and Alison A. Weiss*

Department of Molecular Genetics, Biochemistry, and Microbiology, University of Cincinnati College of Medicine, 231 Albert Sabin Way, Cincinnati, Ohio 45267-0524

Clinical and Vaccine Immunology, 2008

… Unexpectedly, PA alone, previously believed to only mediate entry of lethal factor or edema factor, was found to be toxic to CHO-TEM8 cells; cells treated with PA alone displayed reduced cell growth and decreased metabolic activity. PA-treated cells swelled and became permeable to membrane-excluded dye, suggesting that PA formed cell surface pores on CHO-TEM8 cells….



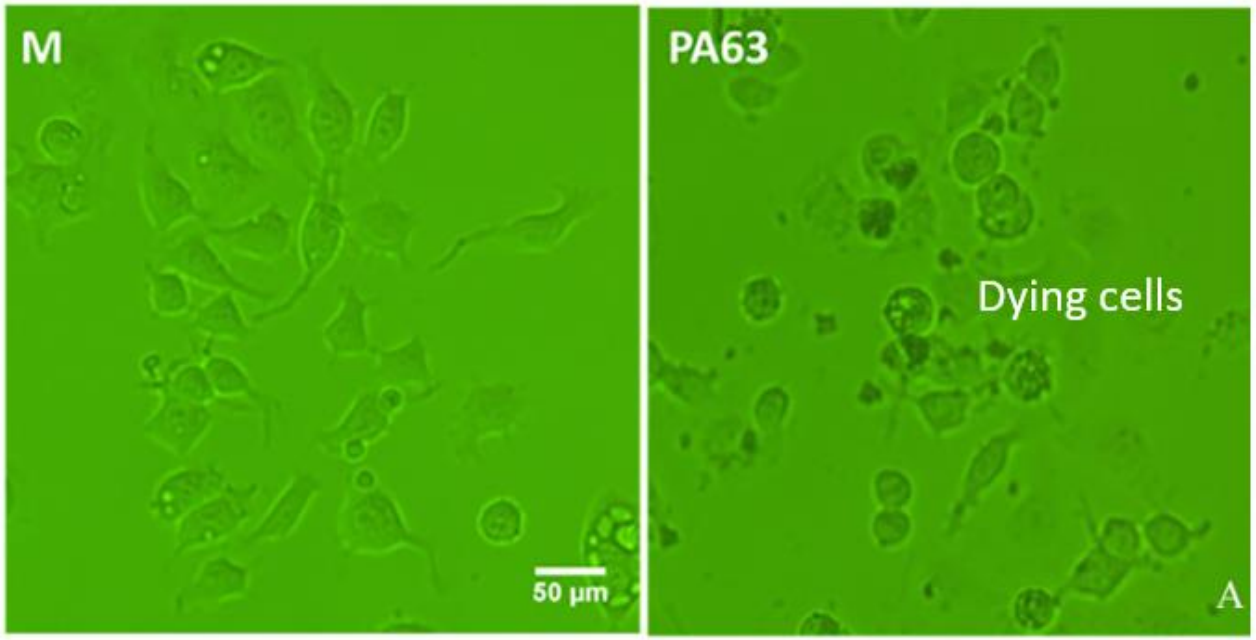
Anthrax Protective Antigen 63 (PA63): Toxic Effects in Neural Cultures and Role in Gulf War Illness (GWI)

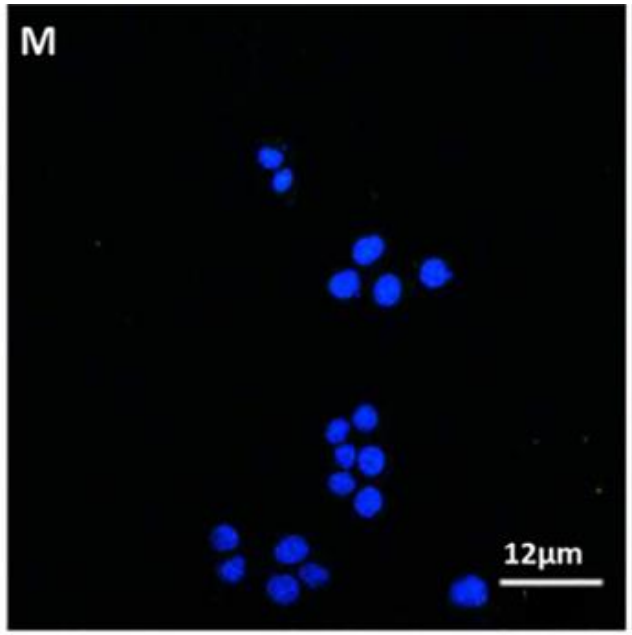
Effie-Photini C Tsilibary[1,2], Eric P Souto[1], Marian Kratzke[1,2], Lisa M James[1,2,3], Brian E Engdahl[1,2,4] and Apostolos P Georgopoulos[1,2,3,5]

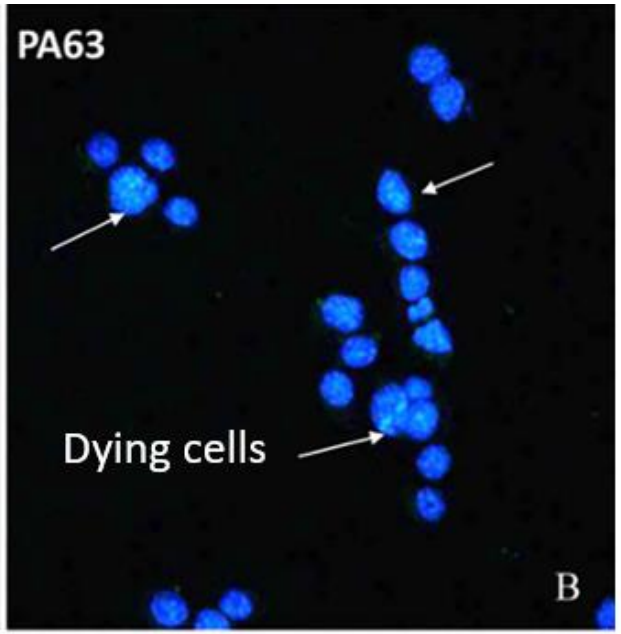
[1]Brain Sciences Center, Department of Veterans Affairs Health Care System, Minneapolis, MN, USA. [2]Department of Neuroscience, Medical School, University of Minnesota, Minneapolis, MN,

Neuroscience Insights, 2022

… We found that, when added in N2A cultures, PA63 toxin led to decreased cell spreading and cell aggregation, leading to apoptosis. The mechanisms of PA63-induced cell damage included compromised cell membrane permeability indicated by enhanced access of propidium iodide in cells. In addition, signaling pathways leading to organization of N2A cytoskeleton were negatively affected, as both actin and microtubular networks were compromised. Finally, the mitochondrial membrane potential was impaired in specific assays. Altogether, these alterations led to apoptosis as a collective toxic effect of PA63 …

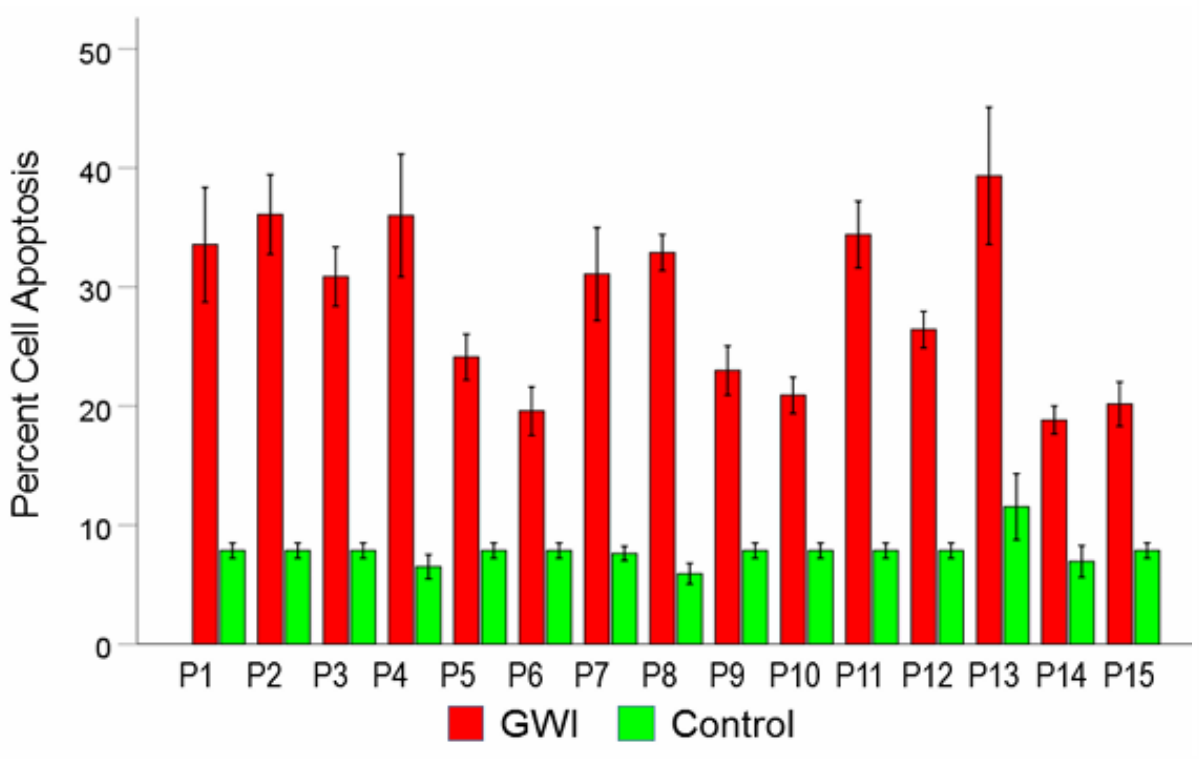


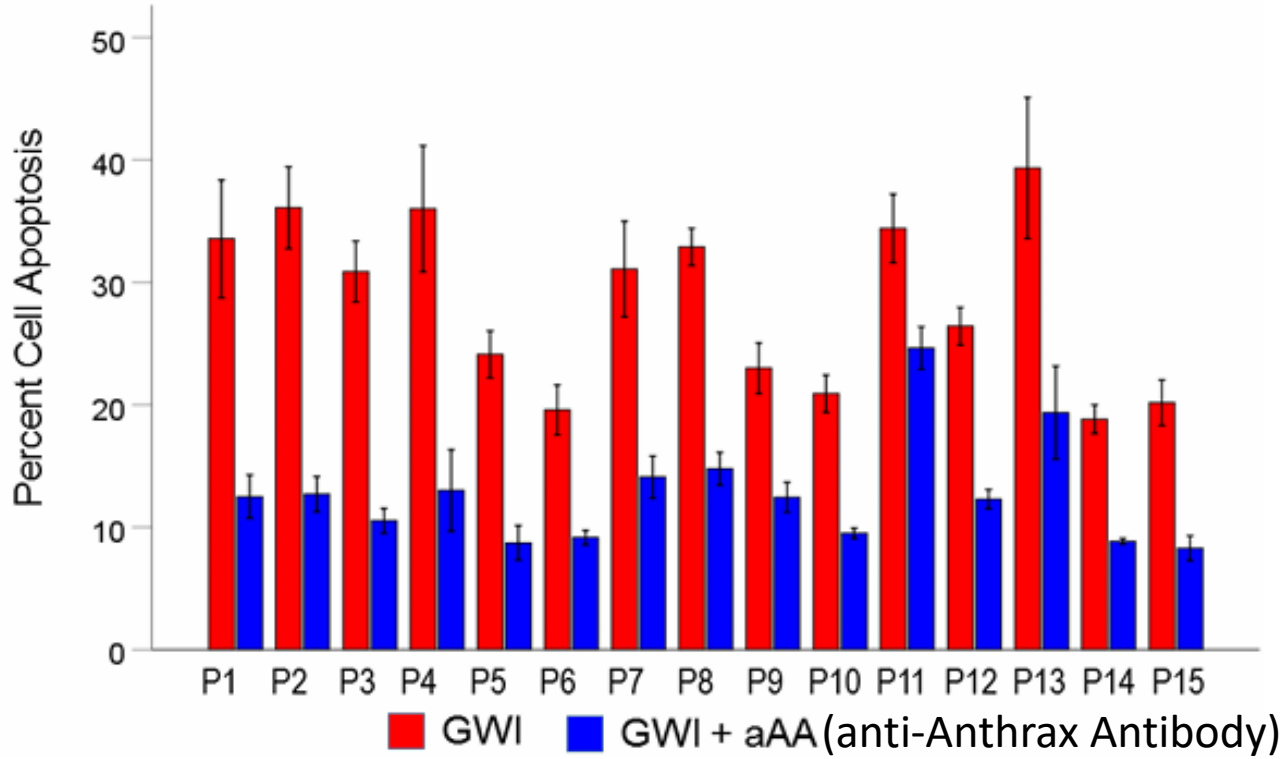




Tsilibary et al., 2020

Anthrax Vaccine Antigen Induces Cell Death (Apoptosis)





Tsilibary et al., Neuroscience Insights, 2022

vaccines

June 4, 2024

MDPI

Article

Anthrax Vaccination, Gulf War Illness, and Human Leukocyte Antigen (HLA)

Lisa M. James [1,2,3,*], Adam F. Carpenter [1,4], Brian E. Engdahl [1,2,5], Rachel A. Johnson [1], Scott M. Lewis [1,4] and Apostolos P. Georgopoulos [1,2,3,4]

The GWI and HLA Research Groups, Brain Sciences Center, Department of Veterans Affairs Health Care System, Minneapolis, MN 55417, USA

… We report on a highly significant, positive association between anthrax vaccination and occurrence of Gulf War Illness (GWI) in 111 Gulf War veterans (42 with GWI and 69 controls). GWI was diagnosed in 47.1% of vaccinated veterans but only in 17.2% of non-vaccinated veterans (Pearson 2 =7.08, p = 0.008; odds ratio = 3.947; relative risk = 2.617), with 1.6x higher GWI symptom severity in vaccinated veterans (p = 0.007, F-test in analysis of covariance)…

GULF WAR ILLNESS / CHRONIC MULTISYMPTOM ILLNESS:
A CURRENT CONCERN

Iraq and Afghanistan Veterans report symptoms consistent with chronic multisymptom illness one year after deployment

Lisa M. McAndrew, PhD;[1–3*] Drew A. Helmer, MD, MS;[1,3] L. Alison Phillips, PhD;[4] Helena K. Chandler, PhD;[1] Kathleen Ray, PhD;[1] Karen S. Quigley, PhD[5]

[1]War Related Illness and Injury Study Center, Department of Veterans Affairs (VA) New Jersey Health Care System, East Orange, NJ;

Journal of Rehabilitation Research and Development, 2016

…Many Veterans returning from service in Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) experience chronic pain. What is not known is whether for some OIF/OEF Veterans this pain is part of a larger condition of diffuse multisystem symptoms consistent with chronic multi symptom illness (CMI). We use data from a prospective longitudinal study of OIF/OEF Veterans to determine the frequency of CMI. We found that 1 yr after deployment, 49.5% of OIF/OEF Veterans met criteria for mild to moderate CMI and 10.8% met criteria for severe CMI. Over 90% of Veterans with chronic pain met criteria for CMI. CMI was not completely accounted for either by posttraumatic stress disorder or by pre deployment levels of physical symptoms. Veterans with symptoms consistent with CMI reported significantly worse physical health function than Veterans who did not report symptoms consistent with CMI. This study suggests that the presence of CMI should be considered in the evaluation of OIF/OEF Veterans. Further, it suggests that the pain management for these Veterans may need to be tailored to take CMI into consideration…

vaccines

February 3, 2024

MDPI

Review

Anthrax Vaccines in the 21st Century

Apostolos P. Georgopoulos [1,2,3,4,*] and Lisa M. James [1,2,3]

The GWI Working Group, Brain Sciences Center, Department of Veterans Affairs Health Care System, Minneapolis, MN 55417, USA

…Vaccination against Bacillus anthracis is the best preventive measure against the development of deadly anthrax disease in the event of exposure to anthrax either as a bioweapon or in its naturally occurring form. Anthrax vaccines, however, have historically been plagued with controversy, particularly related to their safety. Fortunately, recent improvements in anthrax vaccines have been shown to confer protection with reduced short-term safety concerns, although questions about long-term safety remain. Here, we (a) review recent and ongoing advances in anthrax vaccine development, (b) emphasize the need for thorough characterization of current (and future) vaccines, (c) bring to focus the importance of host immunogenetics as the ultimate determinant of successful antibody production and protection, and (d) discuss the need for the systematic, active, and targeted monitoring of vaccine recipients for possible Chronic Multisymptom Illness (CMI)…

SUMMARY

- Anthrax vaccine antigen (AVA) is toxic
- AVA is present in the blood of GWI veterans – a very persistent antigen!
- The variety of cellular functions directly damaged by AVA (increased membrane permeability, disrupted cytoskeleton integrity, mitochondrial dysfunction) could account for the fatigue (mitochondrial dysfunction), myalgia (same), and neurocognitive-mood symptoms (dysfunction of brain neural networks)
- The cell death (apoptosis) induced by AVA could account for brain atrophy (direct loss of neurons), chronic inflammation, and autoimmunity
- The AVA chronic toxic effects, in combination, could contribute/account for symptoms from other organs (gastrointestinal, respiratory, skin)
- CONCLUSION: The continuous presence over the years of the AVA can explain much of the diverse GWI/CMI symptomatology

Q & A

- Q1: Most GW veterans who received AVA did dot develop GWI. Why some Veterans did and others did not?
- A1: Those who did not develop GWI were able to make antibodies against AVA; those who developed GWI could not make antibodies against AVA, hence it persisted.

- Q2: Why GWI Veterans could not make antibodies against AVA?
- A2: Because they lacked the immune genes needed to make specific antibodies against AVA

EBioMedicine, 2016

ACTION!

- The fact that the continuous presence of AVA is at the root of GWI gives hope for a successful intervention: **Elimination of AVA!**
- An obvious treatment would be the administration of specific (mono- and/or polyclonal) antibodies against AVA. Such antibodies exist but they will need to be tested for safety in standard clinical trials before they are approved by the FDA for GWI treatment
- An alternative intervention would be a one-time plasma exchange that will get rid of the circulating toxic AVA. The procedure is safe (currently performed routinely, e.g. for treating myasthenia gravis) but fairly expensive
- Any intervention that removes the circulating AVA will effectively arrest the ongoing damage but any permanent damage already inflicted by AVA may not be reversible (e.g. brain atrophy) but the healing power of the body cannot be underestimated!

Adverse effects of Gulf War Illness (GWI) serum on neural cultures and their prevention by healthy serum

Apostolos P. Georgopoulos[1,2]*, Effie-Photini C. Tsilibary[1,2], Eric P. Souto[1], Lisa M. James[1,2], Brian E. Engdahl[1,2], Angeliki Georgopoulos[3]

Journal of Neurology and Neuromedicine, 2018

…In contrast to healthy serum, the addition of GWI serum disrupted neural network communication and caused reduced cell growth and increased apoptosis. All of these detrimental effects were prevented or ameliorated by the concomitant addition of serum from healthy GW veterans. These findings indicate that **GWI serum contains neuropathogenic factors that can be neutralized by healthy serum. We hypothesize that these factors are persistent antigens circulating in GWI blood that can be neutralized, possibly by specific antibodies present in the healthy serum**, as proposed earlier… (James et al. 2017)

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Thank you!