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Gulf War Illnesses are autoimmune conditions caused by the direct effect of the nerve gas prophylaxis drug (pyridostigmine bromide) on anergic immune system lymphocytes

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A B S T R A C T

Immune system dysregulation in 1991 Gulf War Veterans was caused in part by the nerve gas prophylactic drug pyridostigmine bromide (PB) by direct agonist activation of muscarinic receptors on anergic B and T lymphocytes, leading to multiple types of autoimmune illnesses, and this effect may have been potentiated by combat stress.

Roughly one third of the 700,000 veterans from the 1991 Gulf War continue to be seriously ill [1–3]. The Institute of Medicine (now the National Academy of Medicine) suggested the name “Gulf War Illness” (GWI) for these conditions [4]. Illnesses in these veterans appear to be due to inflammatory conditions indicated by animal models [5,6] and human studies [7,8] and, in addition, reports suggest the adaptive immune system is dysregulated in these veterans [9,10] suggesting autoimmunity [11]. This is consistent with the chronic nature of GWI which has persisted for nearly thirty years.

Anergy in immune T and B cells is a state in which self-reacting (potentially autoimmunity causing cells) are inactivated instead of being eliminated [12,13]. Anergy is a reversible process which could potentially lead to autoimmunity [13–16]. Because about 30% of 1991 Gulf War veterans have a chronic condition which may be an inflammatory or actual autoimmune condition called Gulf War Illness (GWI) an understanding of the cause of GWI might help us understand other immune related illnesses.

Pyridostigmine bromide (PB) (a carbamate cholinesterase inhibitor, similar to a common class of insecticide) was ingested by a large proportion of 1991 Gulf War troops in an attempt to protect them from the effects of nerve gas exposure [1]. It is logical that the recognition and binding site of acetylcholinesterase (ache) and acetylcholine receptors would have properties that would allow some ache inhibiters to also bind to the acetylcholine receptors. PB may have direct muscarinic agonist actions in addition to its (ache) action [17,18] and muscarinic receptors can activate PI3K (phosphatidylinositol 3-kinase) resulting in elevated inositol 3,4,5 phosphate [19].

B-lymphocytes have functional muscarinic receptors [20] and it is reasonable to hypothesize the cells have conserved downstream effector cascades as in astrocytoma cells [19]. Franks and Cambier [21] suggested the over-production of inositol 3,4,5 phosphate PI [3–5] P3 leads to a loss of anergy.

The hypothesis presented here therefore is that PB, a prime suspect in GWI [1], directly reversed the state of anergy in lymphocytes of 1991 Gulf war troops. Because 40% of healthy human B-cells may be anergic [16] one would expect a wide spectrum of outcomes from a general reversal of immune system anergy. In addition to understanding how a “simple” environmental component might alter immune function, a positive aspect of understanding ways to reverse anergy in T or B cells that are potentially reactive to cancer cells might be useful in cancer therapy [22].

Much of the research on PB and GWI suggests that synergism of PB's effects by pesticides and other stressors may have contributed to GWI [23]. For example, PB toxicity to mice was found to be potentiated by beta adrenergic drugs [24]. Beta-adrenergic agonists have anti apoptotic actions in airway eosinophils of BALB/c mice in a PI3K-dependent manner [25]. Thus, it is possible that muscarinic and beta adrenergic pathways converge within lymphocytes and that PB muscarinic effects on anergy would be potentiated by beta adrenergic activity, such as in combat induced stress.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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