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Abnormal brain response to cholinergic challenge in chronic encephalopathy from the 1991 Gulf War

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Abstract

Several case definitions of chronic illness in veterans of the 1991 Persian Gulf War have been linked epidemiologically with environmental exposure to cholinesterase-inhibiting chemicals, which cause chronic changes in cholinergic receptors in animal models. Twenty-one chronically ill Gulf War veterans (5 with symptom complex 1, 11 with complex 2, and 5 with complex 3) and 17 age-, sex- and education-matched controls, underwent an 99mTc-HMPAO-SPECT brain scan following infusion of saline and >48 h later a second scan following infusion of physostigmine in saline. From each SPECT image mean normalized regional cerebral blood flow (nrCBF) from 39 small blocks of correlated voxels were extracted with geostatistical spatial modeling from eight deep gray matter structures in each hemisphere. Baseline nrCBF in symptom complex 2 was lower than controls throughout deep structures. The change in nrCBF after physostigmine (challenge minus baseline) was negative in complexes 1 and 3 and controls but positive in complex 2 in some structures. Since effects were opposite in different groups, no finding typified the entire patient sample. A hold-out discriminant model of nrCBF from 17 deep brain blocks predicted membership in the clinical groups with sensitivity of 0.95 and specificity of 0.82. Gulf War-associated chronic encephalopathy in a subset of veterans may be due to neuronal dysfunction, including abnormal cholinergic response, in deep brain structures.

Keywords: Tomography, emission-computed, single-photon; Physostigmine; Brain diseases; Regional blood flow; Persian Gulf syndrome; Veterans

1. Introduction

The nature and causes of the chronic multisymptom illness in veterans of the 1991 Gulf War, officially designated *undiagnosed illness* by the U.S. Department of Veterans Affairs (VA) (Department of Veterans

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Affairs, 2001), remain controversial. Factor analysis of veterans' typical symptoms have most commonly identified three distinct symptom complexes including a mild cognitive disturbance (complex 1), a more debilitating neurocognitive state with confusion and vestibular ataxia (complex 2), and a somatic pain condition with continuous joint and muscle aching and cutaneous sensory complaints (complex 3)—with all three groups sharing chronic muscle fatigue, fever, diarrhea, and middle and terminal insomnia, suggesting an overall syndrome with variants (Haley et al., 1997b; Fukuda et al., 1998; Haley, 1999a; Ismail et al., 1999; Haley, 1999b; Haley et al., 2001; Cherry et al., 2001a,b; Bourdette et al., 2001; Kang et al., 2002). Intense debate continues over whether these symptom complexes represent unique war-related syndromes reflecting identifiable pathophysiologic mechanisms (Haley, 1997; Landrigan et al., 1998; Binns et al., 2004; Gray et al., 2004). The environmental risk factors most commonly linked epidemiologically with the various case definitions include organophosphate pesticides, pyridostigmine bromide anti-nerve agent medications, and low-level sarin nerve gas in fallout from Coalition bombing of Iraqi ammunition storage sites—all cholinesterase-inhibiting cholinergic stimulants (Golomb, 2008). Numerous animal experiments, recently reviewed by a Federal advisory committee (Binns et al., 2004), have demonstrated chronic brain changes, including alteration of cholinergic receptors (Henderson et al., 2001; Henderson et al., 2002), from exposure to these chemicals either alone or in synergistic combinations. More recently, brain-imaging studies have demonstrated reduced structural volume and fractional anisotropy in magnetic resonance imaging of brain in Japanese victims of the 1995 sarin nerve agent attack in the Tokyo subway (Yamasue et al., 2007), and reduced structural volumes in U.S. Gulf War veterans potentially exposed to sarin nerve agent release from ammunition dump demolition events immediately after the 1991 Gulf War (Heaton et al., 2007). Both studies found the degree of brain changes to be correlated with measures of the degree of sarin exposure (e.g., acute blood cholinesterase activity levels and estimated atmospheric concentrations from dispersion models). To test the plausibility of an organophosphate/cholinesterase-inhibitor etiology for chronic encephalopathy in Gulf War veterans, we performed an experiment in which we stimulated a thoroughly studied group of chronically ill Gulf War veterans and unaffected control veterans with the short-acting cholinesterase-inhibiting drug physostigmine and assessed the effects of the resulting cholinergic challenge on normalized regional cerebral blood flow (nrCBF) measured by single photon emission computed tomography (SPECT). Our hypothesis was that, if a 1991 exposure to cholinesterase-inhibiting chemicals had altered cholinergic receptors or their downstream effecter systems in neurons, the brain activity of affected veterans would respond differently to a cholinergic challenge from that of normal veterans with intact cholinergic systems. To address our pre-stated hypothesis (Haley et al., 2000b; Meyerhoff et al., 2001; Menon et al., 2004), this article investigates patterns of brain function in deep gray matter structures.

2. Methods

2.1. Subjects

The subjects were selected from members of the U.S. Naval construction battalion surveyed in 1995–1996 in whom the three Gulf War symptom complexes were defined by factor analysis of symptoms (Haley et al., 1997b, 2001). Symptom complex 1 ("impaired cognition") is best characterized by distractibility, forgetfulness, feeling depressed, and excessive daytime sleepiness (Haley et al., 2001), and was epidemiologically associated with wearing flea collars containing organophosphate pesticide (Haley and Kurt, 1997). Symptom complex 2 ("confusion–ataxia") involved reduced intellectual functioning, confusion, vestibular ataxia/vertigo attacks, and occasional disorientation (Haley et al., 2001), and was associated epidemiologically with exposure to low-level chemical nerve agent in fallout from bombing of Iraqi ammunition depots and adverse effects of pyridostigmine anti-nerve agent prophylaxis (Haley and Kurt, 1997). Symptom complex 3 ("central pain") involved joint pain in extremities, neck and shoulders, myalgias in arms, and paresthesias/numbness in extremities (Haley et al., 2001), and was associated with more frequent, heavy application of highly concentrated insect repellant and adverse effects of pyridostigmine (Haley and Kurt, 1997). Symptom complex 2 carried the greatest functional impairment (Haley et al., 1997b, 2002).

Eleven subjects with symptom complex 2, five each with symptoms complexes 1 and 3, and 17 age-, sex- and education-matched control veterans participated in this SPECT brain scanning experiment between December 1997 and June 1998. One additional symptom complex 2 subject was excluded from the analysis because he had undergone chemotherapy for lymphosarcoma, which affected the SPECT results. Prior case-control studies involving these subjects identified differences from controls in brain metabolism measured by magnetic resonance spectroscopy (Haley et al., 2000b), central