given s.c. injections of 5mg/kg CP or vehicle (100% DMSO) for 5 consecutive days at 1mg/mL. Extracellular electrophysiology was performed in the CA3-CA1 region of the hippocampus 2-7 days (acute effects) or 3 months (delayed effects) following the last injection. Changes in basal synaptic transmission were measured using input/output curves (0-5mA) while short-term and long-term plasticity were measured using paired-pulse and 100Hz stimulation, respectively. At 3 months, changes in frequency and amplitude of spontaneous miniature excitatory currents (mEPSCs) were measured using whole-cell patch clamp of CA1 neurons in the presence of 100µM picrotoxin and 1µM TTX. Results: Acute effects of CP exposure resulted in a slight increase in excitatory synaptic drive at hippocampal CA3-CA1 synapses. However, delayed effects of CP exposure reduced basal synaptic strength by 51.7% compared to vehicle controls. No difference in short-term or long-term plasticity was found at either time point. At 3 months, mEPSC frequency, but not amplitude, was decreased by 56.5% in CP treated mice compared to controls, suggesting that CP treatment induces a delayed loss of synapse and/or neuron number. Conclusions: Repetitive low-dose exposure to AChE inhibitors leads to delayed chronic impairment of hippocampal function, consistent with symptoms and fMRI findings in human GWI.

ABSTRACT FINAL ID: 2251 Poster Board 446
TITLE: Mechanisms of dysregulation of dopamine neurotransmission by cholinesterase-inhibitors: implications for Gulf War illness
AUTHORS/INSTITUTIONS: M. Torres-Altoro, J.A. Bibb, Psychiatry, UT Southwestern, DAllas, TX; M. Goldberg, Neurology, UT Southwestern, Dallas, TX; J.P. O'Callaghan, NIOSH, CDC, Morgantown, WV; R.W. Haley, Epidemiology/Int Med, UT Southwestern, Dallas, TX
KEYWORDS: Anticholinesterase pesticides, brain dopamine, Gulf War.
ABSTRACT BODY: Abstract Body (Late Breaking Submission): Rationale: Gulf War illness (GWI) is linked epidemiologically with exposure to acetylcholinesterase (AChE)-inhibiting chemicals. In comparisons of ill and well GW veterans, magnetic resonance spectroscopy found metabolite abnormalities in basal ganglia associated with increased central dopamine turnover, and cholinergic challenge with physostigmine caused abnormal cholinergic response in caudate, putamen and globus pallidus. From these findings, we hypothesized that Gulf War Illness (GWI) involves dysregulation of dopamine neurotransmission in the mesocorticolimbic reward and motor circuitry of the basal ganglia, which contributes emotional and visceral nervous system processing. Methods and Results: In an animal model of GWI mice were repetitively exposed to the AChE inhibitors chorpyrifos (CP) and/or pyridostigmine bromide (PB). Repetitive CP exposure increased striatal PKA-dependent phosphorylation of the D1 dopamine receptor downstream effector Ser845 of the GluR1 subunit of the AMPA receptor. Treatment of striatal slices with CP induced a dose-dependent increase in phospho-Ser845 GluR1 and phospho-Thr34 DARPP-32, which was blocked by a D1 antagonist. These effects were also induced by PB. Activation of the D1 dopamine receptor/cAMP/PKA cascade is regulated by the neuronal protein kinase, Cdk5. Interestingly, brain slice treatment with CP induced calpain-dependent conversion of the Cdk5 activating cofactor p35 to p25, a neuronal injury marker. Systemic exposure to PB for 10 days followed by a 4-week delay caused p25 formation in the prefrontal cortex. Finally, treatment of mice with a chronic low-dose combination of CP and PB reduced concentrations of dopamine and its metabolites DOPAC and HVA, and increased dopamine turnover, in the olfactory bulb. Conclusion: Repetitive exposure to AChE-inhibitors causes dopamine neurotransmission abnormalities, possibly contributing to brain dysfunction in GWI.

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