Chlorpyrifos Oxon Primes Microglia: Enhanced LPS-Induced TNFα Production

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Microglia, the resident innate immune cells of the brain, respond to various environmental stimuli, including factors from surrounding tissue and from systemic inputs. These stimuli impact microglial function in both health and disease. Increasing evidence implicates microglia and neuroinflammation in Gulf War illness (GWI) pathology. Gulf War illness is an untreatable chronic multi symptomatic disorder that affects about 30% of Gulf War veterans. It has been proposed that "multiple hits" from exposure to various environmental neurotoxicants such as Chlorpyrifos (CPF), an organophosphate pesticide, combined with low inflammation may initiate exaggerated and persistent central nervous system (CNS) pathology to drive GWI. CPF oxon, an active metabolite of CPF, is associated with deleterious CNS effects, but the role of microglia behind this phenomenon is not fully understood.To investigate the effects of CPF oxon on microglia, we assessed microglial ROS, pro-inflammatory cytokine factors, and NF-κB p50 DNA binding activity in the presence of CPF oxon. HAPI microglia cells were treated with CPF oxon (1μM-1nM), which resulted in a dose dependent increase in H_2O_2 production at 3 hours and elevated superoxide at 30 minutes. CPF oxon failed to initiate TNFα and nitric oxide from microglia cultures. However, CPF oxon significantly decreased NF-κB p50 binding to DNA in microglia, a key redox signaling mechanism linked to microglial priming. Consistent with this premise, pre-treatment with CPF oxon (0.5μM) amplified LPS-induced TNFα production in microglia and neuron-glia cultures. Moreover, when CPF oxon and LPS challenged cells were pre-treated with DPI, a NOX2 inhibitor, we found a significant reduction in TNFα response when compared to non-treated cells, supporting that NOX2 may regulate CPF oxon priming in microglia. These data suggest that CPF oxon may induce ROS production in microglia to reprogram these cells to become more sensitive to pro-inflammatory stimuli (priming).