Poster

809. Neuroinflammation: General

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Title: Chronic corticosterone primes the brain response to select neuroinflammatory agents by overexpression of Toll-like receptor 2 and S100A8: a potential role for microglia

Authors: *L. T. MICHALOVICZ, A. R. LOCKER, K. A. KELLY, D. B. MILLER, J. P. O'CALLAGHAN;
CDC-NIOSH, Morgantown, WV

Abstract: Neuroinflammation is commonly associated with chemically-induced neurotoxicity. We recently demonstrated that chronic exposure to the classic anti-inflammatory glucocorticoid, corticosterone (CORT), can markedly exacerbate, or “prime”, the neuroinflammatory response to select compounds (e.g., neurotoxicants or inflammogens). The mechanism by which this exacerbation is achieved is not yet understood. Here, we have exposed adult male C57BL/6J mice to several known neurotoxicants/AChE inhibitors/inflammogens that cause differential inflammatory responses following CORT pretreatment: methamphetamine (METH), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), diisopropyl phosphorofluoridate (DFP), chlorpyrifos

(CPO), pyridostigmine bromide (PB), lipopolysaccharide (LPS), and polyinosinic:polycytidylic acid (PIC). While a single exposure to these agents increases the expression of inflammatory cytokines in the brain (with the exception of PB), chronic (4-7 days) exposure to CORT (200 mg/L) in the drinking water prior to treatment enhanced the METH, DFP, CPO, and LPS induced neuroinflammation. The extension of this CORT effect across these multiple models, including those that cause neuronal damage and those that do not, suggests that the glial rather than neuronal response to the compounds is important for the proinflammatory effects of CORT. Toll-like receptors (TLRs) have been strongly implicated in glial priming of the neuroinflammatory response. Thus, we investigated whether TLR expression was altered in the brain in parallel with enhanced neuroinflammation. TLR2 was positively associated with the CORT neuroinflammatory priming effect exhibiting significant overexpression in METH, DFP, CPO, and LPS treated mice, but was unchanged, or even downregulated, in MPTP, PB, and PIC treated animals. In contrast, TLR4 expression was largely unaltered by chronic CORT pretreatment. The S100 calcium-binding protein A8 (S100A8), which has been positively associated with neuroinflammation, showed a similar profile to TLR2 expression across the multiple models, as expression was increased with CORT pretreatment in the brains of METH, DFP, CPO, and LPS exposed animals. While TLR2 expression has been characterized in microglial and astroglial priming, S100A8 overexpression is found in activated microglia, suggesting that microglia may be a primary cell type involved in CORT priming. Our data identify TLR2 and S100A8 as potential biomarkers of CORT priming of the brain inflammatory response, making them potential targets for treating diseases associated with microglial priming, such as Gulf War Illness.

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