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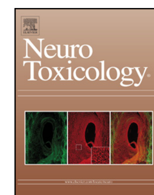

Full length article

Inflammatory and oxidative stress-related effects associated with neurotoxicity are maintained after exclusively prenatal trichloroethylene exposure

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A B S T R A C T

Trichloroethylene (TCE) is a widespread environmental toxicant with immunotoxic and neurotoxic potential. Previous studies have shown that continuous developmental exposure to TCE encompassing gestation and early life as well as postnatal only exposure in the drinking water of MRL+/+ mice promoted CD4^{+} T cell immunotoxicity, glutathione depletion and oxidative stress in the cerebellum, as well increased locomotor activity in male offspring. The purpose of this study was to characterize the effects of exclusively prenatal exposure on these parameters. Another goal was to investigate potential plasma oxidative stress/inflammatory biomarkers to possibly be used as predictors of TCE-mediated neurotoxicity. In the current study, 6 week old male offspring of dams exposed gestationally to 0, 0.01, and 0.1 mg/ml TCE in the drinking water were evaluated. Our results confirmed that the oxidized phenotype in plasma and cerebellum was maintained after exclusively prenatal exposure. A Phenotypic analysis by flow cytometry revealed that TCE exposure expanded the effector/memory subset of peripheral CD4^{+} T cells in association with increased production of pro-inflammatory cytokines IFN-γ and IL-17. Serum biomarkers of oxidative stress and inflammation were also elevated in plasma suggesting that systemic effects are important and may be used to predict neurotoxicity in our model. These results suggested that the prenatal period is a critical stage of life by which the developing CNS and immune system are susceptible to long-lasting changes mediated by TCE.

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1. Introduction

The generation of reactive oxygen species and/or depletion of the glutathione anti-oxidant system as evidenced by a decrease in the active form of glutathione (GSH) and an increase in the inactive oxidized disulfide (GSSG), enhances susceptibility to oxidative stress leading to organ-specific cell damage (Biswas et al., 2006; Bobyn et al., 2002; Filomeni et al., 2002). This is especially evident during development and early life stages (Maffi et al., 2008; McLean et al., 2005; Noble et al., 2005), and may represent a key process by which environmental toxicants influence neurotoxicity (Costa et al., 2015). Glutathione, the major intracellular anti-oxidant in the brain, is derived from the transsulfuration pathway that intersects with the methionine cycle [reviewed in Folate, 2002]. Methionine forms *S*-adenosylhomocysteine (SAM) which, through the transfer of its methyl group, is converted to *S*-adenosylmethionine (SAH) and homocysteine. Homocysteine has an alternative fate. It can regenerate methionine for an additional cycle, or it can be used to produce cysteine which can feed glutathione synthesis. Thus, from a functional standpoint, deficits in any of these metabolites could lead to neurotoxicity by promoting cellular differentiation, gene expression, DNA methylation, and oxidative stress.

Aside from oxidative stress, inflammation including peripheral immune activation and/or the cytokines they release can also adversely impact CNS responses (Anthony et al., 2011; Deledi et al., 2015). These cells and their mediators apparently cross the blood-brain-barrier made more permeable by inflammation (Stolp et al., 2005) to promote neuroinflammation and alter behavior (Wilson et al., 2002). Increased maternal cytokine release occurring during the perinatal period has been shown to increase the risk of

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offspring developing neurologic disease in adulthood (Hagberg et al., 2015). Similarly, rodent models of maternal infection resulting in increased cytokines have been experimentally linked with adverse neurologic outcomes in offspring (Malkova et al., 2012). Immune activation can also activate the kynurenine pathway (*i.e.*, a by-product of the amino acid tryptophan) implicated in major depressive disorder (Hufner et al., 2015), as well as the release of oxidative stress/inflammatory mediators such as 3-chlorotyrosine, by certain immune cells (Knutson et al., 2013). Thus, systemic inflammation immune activation, and oxidative stress are closely linked and may act in concert to promote neurotoxicity.

Environmental toxicants with the ability to promote oxidative stress and inflammatory responses may be important from a neurotoxicological standpoint. One such toxicant is the organic solvent and environmental pollutant trichloroethylene (TCE). TCE is a widespread contaminant that has been used for several decades in many industrial, commercial, medical, and consumer applications. TCE use has declined in the US in recent years. However, due to improper disposal practices, this chemical has become a persistent soil and water pollutant, and areas of TCE contamination are still being revealed. Based on likelihood of exposure together with negative health impact TCE is consistently ranked 16th out of 275 pollutants on the Superfund list of hazardous chemicals (ASTDR, 1997). Thus, human exposure to TCE remains a significant public health concern, and there is clearly a need to study the potential adverse health effect of TCE (Chiu et al., 2013).

Several studies have implicated the brain and immune system, namely $CD4^+$ T cells, as targets of developmental TCE toxicity. Children exposed to TCE beginning *in utero* to a TCE-contaminated water supply had altered ratios of T cell subsets indicating T cell hyperactivity (Byers et al., 1988). We and others have shown that TCE promoted expansion of activated/memory $CD4^+$ T cells with a Th1-like pro-inflammatory phenotype (Peden-Adams et al., 2006; Blossom and Doss, 2007; Blossom et al., 2008; Gilbert et al., 2014). In terms of neurotoxicity, studies by our lab and others have shown cerebellar and hippocampal neurotoxicity with exposure during the perinatal and postnatal periods of development associated with decreased learning and increased locomotor and exploratory activity (Blossom et al., 2012, 2013; Taylor et al., 1985; Isaacson et al., 1990). Children of mothers working with TCE during pregnancy had poorer visual acuity, as well as impaired motor coordination and behavior characterized by inattention and hyperactivity (Laslo-Baker et al., 2004; Till et al., 2001). The mechanism by which developmental exposure to TCE imparts neurotoxicity is largely understudied. Several studies have shown that TCE induces oxidative stress (Ogino et al., 1991; Channel et al., 1998; Wang et al., 2009). We have focused on oxidative stress responses in the brain associated with developmental TCE exposure.

Before mechanism can be addressed, it is important to determine the most sensitive window of susceptibility for developmental TCE toxicity. Development of the immune system and the CNS in both humans and rodents spans throughout gestation and postnatally until adulthood suggesting that these systems, due to their extended period of maturation, may be particularly vulnerable to environmental stressors (Dietert and Piepenbrink, 2006; Rice and Barone, 2000). Although many important neurodevelopmental processes are shaped prenatally (Lindahl et al., 2008), the brain undergoes significant development postnatally, including transient periods of rapid or slow growth between birth and young adulthood (Gottlieb et al., 1977; Clancy et al., 2007; Dumas, 2005). Thus, we hypothesized that the impact of TCE after prenatal-only exposure would be less robust than observed at other developmental periods. In contrast to our expectations, the findings of this study revealed that many effects associated with postnatal and/or early life exposure were maintained with prenatal TCE exposure. This study also revealed several potential plasma biomarkers that may potentially be used to monitor TCE-induced effects in the brain.

2. Materials and methods

2.1. Mice and TCE exposure

Gestational exposure to TCE in MRL+/+ mice has been described in detail (Blossom et al., 2008; Gilbert et al., 2014). Pregnant females were assigned to 3 groups by stratified randomization and given ultrapure water with 0 (control), 0.01, or 0.1 mg/ml TCE (purity 99+% purchased from Sigma, St. Louis, MO). Water with 0 (control), 0.01, or 0.1 mg/ml TCE also contained 1% Alkamuls EL-620, an emulsifier consisting of ethoxylated castor oil (Rhone-Poulenc, Cranbury, NJ), a reagent used to solubilize the TCE. Maternal exposure to TCE-containing drinking water ended at birth [*i.e.*, postnatal day zero (PND0)]. Litters were standardized at birth to consist of no more than 8 pups per litter. At ~6 weeks of age, one randomly selected male mouse from each litter was used for all assays described below. All studies were approved by the Animal Care and Use Committee at the University of Arkansas for Medical Sciences.

2.2. Open field activity

All open field tests were conducted and analyzed using EthoVision XT 8.0 video- tracking software (Noldus Information Technology, Inc., Leesburg, VA). This system digitizes the video signal obtained from a color LCD camera mounted on the ceiling to determine the spatial coordinates of the mouse's location within the testing arena. From these coordinates, the distance traveled per unit time, the number of times a defined zone is entered and the amount of time within a zone was calculated. The behavioral tests were conducted under standard lighting conditions in an isolated room to minimize the interference of noise. For locomotor activity, mice were placed in an unfamiliar testing arena ($45 \times 45\ cm^2$) and the distance traveled (cm) was measured in a 20 min testing period. Other outcomes in the open field included total time in the center, number of times in the center, latency to enter the center zone, and velocity. Each behavior was calculated by the EthoVision software for each individual mouse.

2.3. HPLC quantification of plasma and cerebellum metabolites

Mice were deeply anesthetized with inhaled isoflurane (Fisher). A blood sample was collected using retro-orbital sampling, placed in heparinized tubes and processed to obtain plasma. Mice were then sacrificed and the cerebellum was dissected from the whole brain tissue and flash frozen in liquid nitrogen. Samples were stored at −80 °C until extraction for metabolite detection. The methodological details have been described previously (Melnyk et al., 1999). The analyses were performed using HPLC with a Shimadzu solvent delivery system (ESA model 580) and a reverse phase C18 column (3 μm; 4.6 × 150 mm, Phenomenex, Inc., Torrance, CA). Brain extracts were directly injected onto the column using a Beckman Autosampler (model 507E). All metabolites were quantified using a model 5200A Coulochem II and CoulArray electrochemical detection system (ESA, Inc., Chelmsford, MA) equipped with a dual analytical cell (model 5010), a 4 channel analytical cell (model 6210) and a guard cell (model 5020). The levels or concentrations of thiol metabolites, methyl group donor metabolites, and oxidative stress biomarkers in cerebellum or plasma were calculated from peak areas and

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