Environmental Toxins Linked to Neurodegeneration and Autism Activate the Brain’s Immune System

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Abstract
Microglia are the primary immune cells of the central nervous system and become activated in response to noxious stimuli, leading to a cycle of inflammation and cell death that has been implicated in the development of Parkinson's disease and autism. This study examines the effects of environmental toxins, at levels commonly found in humans, on microglial cell survival and activation. The toxins used in this study include polybrominated diphenyl ether (PBDE) flame retardants, the food additive propionic acid (PPA), and the organochlorine pesticide dieldrin. These chemicals have been linked to neuronal damage, although their effects on microglial cells have not been fully studied. Our results indicate that microglial cell survival could be decreased by as much as 50% due to exposure to these toxins, without the production of certain cytokines produced by lipopolysaccharide (LPS)-induced activation. These effects are significant as further understanding of the role of microglia in neuronal damage could provide a pharmacologic target for future drug development as well as elucidate the pathology of neurodegenerative diseases.

Disciplines
Pharmacy and Pharmaceutical Sciences

Comments
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Abstract:
Microglia are the primary immune cells of the central nervous system and become activated in response to noxious stimuli, leading to a cycle of inflammation and cell death that has been implicated in the development of Parkinson’s disease and autism. This study examines the effects of environmental toxins, at levels commonly found in humans, on microglial cell survival and activation. The toxins used in this study include polychlorinated diphenyl ethers (PBDEs) flame retardants, the food additive propionic acid (PAA), and the organophosphate pesticide dimethoate. These chemicals have been linked to neuronal damage, although their effects on microglial cells have not been fully studied. Our results indicate that microglial cell survival could be decreased as much as 50% due to exposure to these toxins without the production of certain cytokines produced by lipopolysaccharide (LPS)-induced activation. These effects are significant as further understanding of the role of microglia in neuronal death could provide a pharmacologic target for future drug development as well as elucidate the pathology of neurodegenerative diseases.

Introduction:
In the central nervous system (CNS), microglia are the innate immune cells. Microglia are spread throughout the brain and when resting appear ramified, or branched (See Fig. 1). These branches extend into the surrounding tissue. Microglia wait in this resting state until contact is made with environmental triggers: damaged cells, foreign matter, plaque or other inflammatory triggers (e.g., pathogens or toxic chemicals).

Propionic acid (PAA), a natural component of butter and some cheeses, has been used as a pesticide due to its fungicidal and bactericidal properties. It is also an endogenous metabolite in humans, and as such is exempt from legal residue limits when applied to crops. Moreover, it does not have to undergo typical pesticide toxicity data and testing. PAA is readily able to cross the blood brain barrier and enter the CNS where it has been linked to autism, and has been proven to activate microglial cells in vivo. The molecular effects of this activation are unknown.

PBDE flame retardants are commonly used in many household items, from computers and televisions to carpeting and furniture. They’ve also been found to be increasingly prevalent in the environment, with high levels recorded in soil, animals, and human serum and milk.

PBDE flame retardants are known to cause irreversible neuronal damage. PBDE-47, a common PBDE homolog, has been shown to induce ROS formation in human neutrophil granulocytes and primary rat hippocampal neurons in vitro.

Results:

- Dieldrin (FIGURE 3) significantly reduces microglial cell survival at doses of 10, 20, 30 and 40 uM, with 20 uM being dose-dependent.
- PBDE-47 (FIGURE 4) caused a statistically significant reduction in survival of microglia at a dose of 60 uM
- PAA (FIGURE 5) exposure also caused a significant decrease in microglial cell survival at concentrations of 1.5 and 3.0 mM.
- Neither dieldrin, PBDE-47, nor PAA activate microglia to release the cytokine TNF-α or nitrite, both typical markers of microglial activation.

Conclusion:
Microglia play a major role in immunity for the CNS, and chronic activation due to environmental toxins or neuronal damage has been shown to result in neuronal death and inflammation. This study shows that the environmental toxins dieldrin, PBDE-47 and PAA can cause microglial cell death at physiologically relevant levels, instead of the release of inflammatory cytokines, as commonly seen in response to threatening stimuli in the CNS (e.g., LPS and air pollution). This implies the presence of a separate mechanism of action of these toxins, resulting in cell death. It also implies that microglia may be compromised, and be unable to serve protectively when exposed to certain toxins, leaving neurons vulnerable.

Future directions of study involve exploring the mechanisms of toxin-induced microglial cell death. This includes the measurement of the activity of histone acetyl transferase (HAT) proteins. Histone acetylation allows for DNA to become transcriptional and translatable histories, and so for gene transcription. Preliminary studies have indicated that HAT inhibitors may help protect against toxic-induced microglial cell death. Clarifying the pathways of neurodegeneration due to environmental toxins will offer new targets for investigational drug research.