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Review

The use of glial data in human health assessments of environmental contaminants

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ABSTRACT

Central nervous system (CNS) glia (i.e., astrocytes, microglia, and oligodendrocytes) are essential for maintaining neuronal homeostasis, and they orchestrate an organized cellular response to CNS injury. In addition to their beneficial roles, studies have demonstrated that disrupted glial function can have disastrous consequences on neuronal health. While effects on neuron-supportive glia are important to consider when evaluating neurotoxicity risk, interpreting glial changes is not always straightforward, particularly when attempting to discern pro-neurotoxic phenotypes from homeostatic processes or adaptive responses. To better understand how glia have been characterized and used in human health assessments of environmental contaminants (e.g., chemicals), an evaluation of all finalized assessments conducted by the U.S. Environmental Protection Agency's influential Integrated Risk Information System (IRIS) program between 1987 and 2013 was performed. Human health assessments to date have placed a clear emphasis on the neuronal cell response to potential toxicants, although more recent assessments increasingly include descriptions of glial changes. However, these descriptions are generally brief and non-specific, and they primarily consist of documenting gliosis following overt neuronal injury. As research interest in this topic continues to increase, methods for evaluating changes in glia continue to be expanded and refined, and assessors' confidence in the reliability of these data is likely to rise. Thus, glial data are anticipated to have an increasingly influential impact on the interpretation of neurotoxicity risk and underlying mechanisms. As our understanding of the complex roles these cells play grows, this knowledge is expected to support the inclusion of more extensive and specific descriptions of glial changes, including informed interpretations of the potential impact on CNS health, in future human health assessments.

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1. Introduction

Glia play numerous, critical roles in the maintenance of a healthy human nervous system (recent reviews include (Gallo and Deneen, 2014; Nave and Ehrenreich, 2014; Salter and Beggs, 2014;

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Schafer et al., 2013; Volterra and Meldolesi, 2005)). Astrocytes, which comprise nearly 50% of the total volume of the human brain (Tower and Young, 1973), have been the major focus of research on glia. They have critical responsibilities in the mature central nervous system (CNS), including providing structural and trophic support to neurons, helping to maintain blood–brain barrier (BBB) integrity, and detoxifying potentially harmful cellular waste products from the parenchyma. The traditional function of microglia as the brain's "garbage men" to clear potentially harmful cellular debris and maintain the adult CNS as an immunologically-privileged site has been expanded to situate them as dynamic sentinels of the CNS microenvironment and the first line of defense against injury, as microglia constantly sample the parenchyma and are the first cells to respond to perturbations to brain homeostasis (Davalos et al., 2005; Kettenmann, 2007; Nimmerjahn et al., 2005). In addition, both microglia and astrocytes contribute to neurotransmission and neurogenesis (Halassa et al., 2007; Marin and Kipnis, 2013; Perea et al., 2009; Sierra et al., 2014). A key role for oligodendrocytes in the mature brain is related to the continued remodeling and maintenance of myelin necessary for neuronal plasticity and recovery from demyelination or CNS injury (Kang et al., 2010; Young et al., 2013). Glia also play key roles during development. For example, astrocytes help to regulate developmental synaptogenesis, neurogenesis, and neuronal differentiation, and radial glia (a heterogeneous, non-neuronal cell population related to mature astrocytes) guide neuronal migration (Campbell and Gotz, 2002). Oligodendrocytes are responsible for myelinating the CNS, which allows for efficient and essential nerve conduction, and they may also provide trophic support to developing axons (Mitew et al., 2014). Microglia in the developing brain have multiple functions, including clearance processes related to the removal of excess neurons and synapses (Harry and Kraft, 2012). Taken together, the current understanding of glial cell biology has revealed that these cells are essential for normal nervous system function throughout the entire lifetime, providing multiple cell type-specific windows of potential vulnerability to neurotoxicants.

As our understanding of their functions continues to expand, so too does our understanding of the various ways glia may be implicated in chemical-induced neurotoxicity. Based upon the strengthening evidence linking neurotoxicity and changes in neuron-supportive glia, it is now recognized that adverse health outcomes in humans often involve contributions from dysregulated astrocytes, microglia, and/ or oligodendrocytes. These cells, particularly microglia, have been well-documented to serve as indirect sources of toxicity following neuronal injury (reviewed in the context of neurodegenerative disease by (Block and Hong, 2005; McGeer and McGeer, 2008)), but glia also represent potential primary targets for the toxic actions of chemicals (e.g., disrupted astrocyte homeostasis as a potential mechanism for neurotoxicity following exposure to ammonia (Rangroo Thrane et al., 2013) and methylmercury (Aschner et al., 1990)). Additionally, glia can activate compounds to their neurotoxic moiety (as in the conversion of MPTP to MPP+ by astrocytes (Ransom et al., 1987)). However, a challenge to interpreting the impact of glial responses is a difficulty in discerning pro-neurotoxic phenotypes from compensatory or adaptive mechanisms enacted within these cells. In many cases, these compensatory mechanisms are responses to an initiating insult that are indispensable for damage resolution and recovery.

Improved understanding and careful interpretation of non-neuronal cell responses to environmental chemicals is expected to enhance the evaluation of CNS endpoints in human health assessments, and perhaps inform subsequent dose-response analyses. For example, an understanding of mode-of-action (MOA) can help to identify hazard(s) and reduce uncertainty in the default assumptions used for deriving quantitative risk estimates (e.g., default factors applied to account for animal-to-human or human-to-human variation in responses). At a minimum, incorporating evidence on glial endpoints expands MOA information to allow for a more thorough understanding of how neurotoxicity may develop following chemical exposure. In application, such an understanding could be used to characterize mechanistic events associated with glial changes along the progression towards frank neurotoxic effects (e.g., by using the "adverse outcome pathway" approach; (Ankley et al., 2010)) and help to identify populations that may be at increased risk of developing neurotoxicity following chemical exposure.

As a barometer for how glial data have been incorporated into human health assessments to date, an evaluation of 544 health assessments finalized by the highly influential Integrated Risk Information System (IRIS) Program of the U.S. Environmental Protection Agency (EPA) was performed. IRIS uses the published, peer-reviewed literature to evaluate both the qualitative and quantitative health information on effects from exposure to environmental contaminants of concern. Currently, the IRIS database (http://www.epa.gov/iris/) contains human health effects information on over 550 potentially hazardous substances, the majority of which are environmental chemicals, although the database does include non-chemical contaminants (e.g., diesel exhaust particles). Noncancer health hazards considered in IRIS assessments include nervous system effects, and the IRIS assessment process involves the collection, interpretation, and integration of data on multiple biological endpoints across studies in humans, experimental animals, and in vitro systems to ultimately derive an overall oral reference dose and/ or inhaled reference concentration (RfD and RfC, respectively). These reference values are estimates of the daily exposure to a given agent without appreciable risk of deleterious noncancer health effects during a lifetime.

The current evaluation identifies the future potential for using evidence on glial changes to improve characterization of nervous system effects in chemical assessments. It also highlights difficulties in the interpretation of glial changes from the vantage-point of risk assessors, and it elaborates on the information such data may be able to provide in the future. Based on the database of environmental health studies considered in these types of assessments, research needs that could improve the utility of data on glial responses for characterizing neurotoxic changes and glial endpoints that may best inform future assessments were identified. Overall, the results raise important considerations for future evaluations of evidence on glial changes when assessing human neurotoxicity risk.

2. An evaluation of human health assessments of environmental contaminants

To illustrate how glial data have been used in chemical assessments, IRIS assessments completed between 1987 and 2013 were reviewed using keyword queries for CNS-specific effects involving astrocyte, microglia, and/ or oligodendrocyte contributions. Importantly, these evaluations aimed to broadly identify any chemical that appeared to have some effect on the nervous system, and these results do not necessarily indicate a neurotoxicity hazard was identified. IRIS assessments are described in IRIS Summaries, which include a synopsis of the human health hazards (typically in <10 pages), and some IRIS assessments completed after 1996 include support documents termed IRIS Toxicological Reviews, which comprehensively detail the specifics of the identified health hazards (these can be >100 pages). The specific IRIS Summaries and IRIS Toxicological Reviews searched, as well as the results of those searches, are described in the