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Unmasking silent neurotoxicity following developmental exposure to environmental toxicants

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ABSTRACT

Silent neurotoxicity, a term introduced approximately 25 years ago, is defined as a persistent change to the nervous system that does not manifest as overt evidence of toxicity (i.e. it remains clinically unapparent) unless unmasked by experimental or natural processes. Silent neurotoxicants can be challenging for risk assessors, as the multifactorial experiments needed to reveal their effects are seldom conducted, and they are not addressed by current study design guidelines. This topic was the focus of a symposium addressing the interpretation and use of silent neurotoxicity data in human health risk assessments of environmental toxicants at the annual meeting of the Developmental Neurotoxicology Society (previously the Neurobehavioral Teratology Society) on June 30th, 2014. Several factors important to the design and interpretation of studies assessing the potential for silent neurotoxicity were discussed by the panelists and audience members. Silent neurotoxicity was demonstrated to be highly specific to the characteristics of the animals being examined, the unmasking agent tested, and the behavioral endpoint(s) evaluated. Overall, the experimental examples presented highlighted a need to consider common adverse outcomes and common biological targets for chemical and non-chemical stressors, particularly when the exposure and stressors are known to co-occur. Risk assessors could improve the evaluation of silent neurotoxicants in assessments through specific steps from researchers, including experiments to reveal the molecular targets and mechanisms that may result in specific types of silent neurotoxicity, and experiments with complex challenges reminiscent of the human situation.

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1. Introduction

"Silent neurotoxicity", also called silent toxicity or silent damage to the nervous system, represents a persistent biochemical change or morphological injury to the nervous system that does not induce overt evidence of toxicity (i.e. remains clinically unapparent) unless unmasked by experimental or natural processes (Reuhl, 1991; Grandjean, 2008; Giordano and Costa, 2012). This concept has been described in association with numerous neurotoxic chemicals and neurodegenerative diseases since its first use approximately 25 years ago (Needleman, 1993; Weiss, 1996; Thiruchelvam et al., 2002; Weiss et al., 2002; Costa et al., 2004; Cory-Slechta et al., 2005; Barlow et al.,

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2007; Fan et al., 2011). While silent neurotoxicity might be relevant to a broad range of toxicity mechanisms, and therefore be of concern for many environmental chemicals, it remains poorly understood.

Silent neurotoxicity overlaps with other commonly used terms, including, perhaps most closely, the "2-hit" or "multiple hit" models and hypotheses (including the "neurodevelopmental hypothesis"). Each of these terms describe the occurrence of initial insults that can alter cellular function and prime a system to either make it vulnerable to a subsequent insult(s) or progressively lead to loss of normal function with additional insult(s), with the effects of one insult in isolation being insufficient to induce disease. These theories are based on studies of carcinogenesis, but have been more recently applied to nervous system effects (Nordling, 1953; Armitage and Doll, 1957; Weinberger, 1987; Bayer et al., 1999). Silent neurotoxicity is also related to the phenomena of chemical and non-chemical "interactions" (National Research Council, 2009) and "latent" or "delayed" neurotoxicity (Aldridge et al., 1969). In general, although there may be slight differences in the application of these closely related terms (e.g., emphasis on a period of latency between exposure and the ability to reveal effects; emphasis on a developmental insult; limited to specific types of "unmasking"; etc.), all of these inter-related concepts are attempting to examine and describe neurotoxicity in terms of cumulative effects that may be more relevant to human exposure situations than traditional toxicity testing for effects of a single chemical measured immediately after exposure.

For silent neurotoxicity, in the context of environmental health, a factor that "unmasks" toxicity could be any stimulus that challenges or otherwise adjusts the threshold of a cellular system that is the target of a particular environmental agent. Some examples of "unmasking" agents may include stress, disease, infection, or multiple chemical exposures, while related natural processes could include aging or loss of tolerance. Although the topic of silent neurotoxicity does not represent a new concept (Reuhl, 1991), it is one that persists in the neurotoxicology literature (Giordano and Costa, 2012). Despite the attention given to this topic, our current understanding of the different causes for silent neurotoxicity remains incomplete. While recent research continues to unravel the molecular targets that may be involved for certain types of insults, which is expected to improve our understanding of the molecular mechanisms of developmental neurotoxicity and help to move the field forward (e.g., via construction and sharing of common adverse outcome pathways (Ankley et al., 2010)), identifying potential silent neurotoxicants remains difficult for risk assessors.

This topic was the focus of a symposium held on June 30th, 2014 at the 38th annual meeting of the Developmental Neurotoxicology Society (previously the Neurobehavioral Teratology Society) held in Bellevue, WA from June 28th–July 2nd. The symposium was organized into a series of presentations followed by a facilitated panel discussion with the audience, which was comprised of academicians, federal and state government scientists, industry scientists, and non-government organization representatives. The intent of the discussion was to provide information useful to risk assessors, who often find these data (particularly data related to behavioral changes) difficult to incorporate into their neurotoxicity hazard descriptions. It is clear that the appropriate interpretation of experiments capable of revealing silent neurotoxicity would also be of critical use to decision-makers considering cumulative risk assessment (i.e. the combined risk from multiple agents or stressors, including chemical mixtures as well as non-chemical stressors) and environmental justice scenarios (e.g., improving the decision maker's assessment of effects from disproportionate exposure in low income communities by effectively identifying the most vulnerable subpopulations), two key areas of current interest in the risk assessment field.

From a risk assessment vantage-point, the potential for silent neurotoxicity is concerning for a number of reasons. First, because these types of experiments can be difficult to perform, they are seldom found in the published literature and, when available, they are often focused on narrowly defined, specific research questions that can be difficult to extrapolate to broader exposure scenarios or populations being investigated by the risk assessors. Additionally, experimental animal studies conducted according to guideline protocols (e.g., a developmental toxicity study), which may be viewed as the most desirable studies available for use in risk assessments due to factors such as their use of standardized endpoints and large group sizes, are not designed to detect these types of effects. Taken together, the fact that the overwhelming majority of studies used in risk assessments do not consider multiple insults, or "challenges", in a single model has the potential to result in an underrepresentation of the true potential for developmental neurotoxicity induced by the substance(s) under evaluation. For environmental agents that only exhibit toxicity in the presence of another chemical or non-chemical stressor, if experimental unmasking challenges were not examined, then a neurotoxicity hazard could be considered unlikely based on evidence collected under basal conditions. Since every human exposure scenario involves both chemical and non-chemical stressors, with the right combination the chemical might exhibit effects that wouldn't be identified by experimental studies testing for effects in isolation. Similarly, effects that appear to be "reversible" (i.e. phenotypes that appear to be associated with the presence of the causal agent in the body) may not be used for derivation of toxicity values, even though these agents may have additional latent effects observed only with unmasking. In addition to laboratory-based toxicology experiments, silent neurotoxicity also poses a difficulty for epidemiologic studies. For instance, it might be problematic to link an observed apical effect back to a particular chemical exposure if the investigator does not specifically examine effect modification by the unmasking stimuli revealing the response (e.g., age; other chemical exposures). Finally, a lack of data examining silent neurotoxicity increases the possibility of assessors providing an incomplete description of potentially sensitive subpopulations and lifestages, such as children who experienced prenatal maternal stress (e.g., acute or chronic distress during pregnancy that may result from emotional or physical trauma to the mother) or individuals exposed to a complex mixture containing both the contaminant in question and other agents capable of unmasking neurotoxicity. Overall, this continues to represent a critical and controversial topic for neurotoxicity risk assessment.

2. Summary and critical messages from the symposium presentations

Dr. Aschner introduced the topic by presenting human data from methylmercury (MeHg) poisonings in Minamata, Japan (contaminated fish) and Iraq (contaminated grain). He reflected that exposed victims consistently exhibited a long latent period of weeks to months (or longer) after exposure ended before the onset of behavioral symptoms (Grandjean et al., 1998; Myers et al., 2000; Castoldi et al., 2003). Initially, these latent effects were hypothesized to be due to the slow accumulation of a toxic metabolite, iHg (inorganic mercury), which would vary across individuals depending on their metabolism, and which would be expected to correlate inversely with latency. One would expect the buildup of iHg to be faster at higher levels of MeHg exposure, resulting in a shorter latency period. However, this is not substantiated by the data, with patients experiencing higher MeHg exposure levels failing to show shorter latency periods (Weiss et al., 2002). Interestingly, in at least some cases, the onset of different behavioral phenotypes was shown to occur with different latencies (e.g., visual constriction could be manifest several months after ataxia). While this may illustrate progressive injury to a single cellular system, which seems unlikely for the example above at least, it is probably more likely that this disparity reflects differences in the time-dependence for clinically manifest changes due to effects at different molecular targets, including the dopamine and GABA neurotransmitter systems (Newland et al., 2008). It is also possible that the rate of conversion of MeHg to iHg is rate-limited and therefore iHg is constantly generated at a rate independent of the level of MeHg; however, the literature does not support the underlying