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NeuroToxicology 26 (2005) 491–510

NeuroToxicology

Studying Toxicants as Single Chemicals: Does this Strategy Adequately Identify Neurotoxic Risk?

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Received 27 September 2004; accepted 17 December 2004
Available online 2 February 2005

Abstract

Despite the fact that virtually all chemicals exposure of humans are to mixtures, and that these mixed exposures occur in the context of numerous other risk modifiers, our current understanding of human health risks is based almost entirely on the evaluation of chemicals studied in isolation. This paper describes findings from our collaborative studies that prompt questions about these approaches in the context of neurotoxicology. The first section describes studies investigating the interactions of maternal Pb exposure with maternal stress. Examined across a range of outcome measures, it shows that maternal Pb can modulate the effects of maternal stress, and, conversely, stress modifies the effects of Pb. Further, effects of Pb + stress could be detected in the absence of an effect of either risk factor alone, and, moreover, the profile of effects of Pb alone differs notably from that of Pb + stress. Collectively, interactions were not systematic, but differed by brain region, gender and outcome measure. A second section describes outcomes of studies examining combined exposures to the pesticides paraquat (PQ) and maneb (MB) during development which likewise reveal potentiated effects of combined exposures. They also demonstrate examples of both progressive and cumulative neurotoxicity, including a marked vulnerability following gestational exposure to MB, to the effects of PQ, a pesticide with no structural relationship to MB. The ability of current hazard identification and risk assessment approaches to adequately identify and encompass such effects remains an important unanswered question. One consideration proposed for further evaluating potential interactions that may be of significance for the nervous system is based on a multi-hit hypothesis. It hypothesizes that the brain may readily compensate for the effects of an individual chemical itself acting on a particular target system, but when multiple target or functional sites within that one system are attacked by different mechanisms (i.e., multiple chemical exposures or chemical exposures combined with other risk factors), homeostatic capabilities may be restricted, thereby leading to sustained or cumulative damage.
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Keywords: Chemical mixtures; Risk modification; Neurotoxicity; Risk assessment; Lead; Pesticides; Parkinson's disease; Stress

INTRODUCTION

As based on outcomes from experimental studies, our current understanding of the human health risks associated with exposures to environmental and occupational chemicals has been derived almost entirely from the study of these substances in isolation, i.e., as individual agents. Certainly, the focus on individual chemical agents has been a significant first step in toxicological sciences. Such studies, for example, have been critical in understanding the nature of the adverse effects associated with exposure to an agent, and in identification of the exposure levels at which such

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0161-813X/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuro.2004.12.007

adverse effects are observed. In addition, such studies have, for some toxicants, been instrumental in providing an understanding of the biological mechanism(s) by which the chemical exerts its effects.

From these studies, risk assessments, exposure limits and permissible levels have been established and implemented both for some environmental chemicals and for chemicals used in the workplace. These are empirically derived from the no-observed adverse effect levels (NOAELs) or the lowest observed adverse effect levels (LOAELs) from the associated dose-effect curves. Superimposed upon these NOAELs or LOAELS are various safety or uncertainty factors to accommodate issues such as the potentially enhanced susceptibility of children or the aged to adverse effects, or for differences in species sensitivity, since humans sometimes appear to show greater sensitivity than do experimental species such as mice and rats (Dourson et al., 1996; Rushton and Elliott, 2003). Clearly such regulations have been useful for limiting toxicant exposures and minimizing associated human health effects.

Such a strategy, however, clearly fails to encompass important environmental realities. One such reality is that human chemical exposures rarely occur in isolation, i.e., to individual agents. Indeed, environmental and occupational chemical exposures are to mixtures (Simmons, 1995). Consider an example such as ‘‘air pollution" or even more specifically, $PM_{2.5}$, a mixture of ultrafine particles whose composition differs depending upon geographical location. These exposures to mixtures, moreover, change in composition and level in a dynamic fashion across time.

A second environmental reality is that with respect to human health effects, virtually all chemical exposures occur in a context of a broad array of other risk factors, including genetic background, dietary status, underlying or intercurrent disease states, socioeconomic status, smoking, alcohol consumption, lifestyle, etc. These factors may be risk enhancing (e.g., obesity and cardiovascular disease) or risk mitigating (e.g., lower caloric intake can extend life-span). In some cases, risk factors may even have dual functions. For example, cigarette smoking is known to enhance the risk for lung cancer, but can be protective against Parkinson’s disease (PD) (Abbott et al., 2003; Baldereschi et al., 2003; Lai et al., 2002; Tan et al., 2003). This collective ‘‘context" of risk factors, moreover, also evolves in a dynamic fashion over the lifetime of an individual. These dynamic changes in both exposures and extant risk factors collectively yields a complex set of changing interactions of chemical exposures with risk factors with an ultimate expression manifest in the degree of human health effects. This contrast between the environmental realities and standard risk assessment methodologies forces us to confront at least two important questions. The first is whether extant risk factors, be they other additional chemical exposures or genetic, physiological or lifestyle factors, can modulate the effects of a toxicant, i.e., interact with chemical exposures. If so, then an obvious next question is whether current risk assessment approaches are sufficiently protective to incorporate potential interactive effects of various risk factors. That is, are current hazard identification and/or risk assessment strategies, as based on studies of chemicals in isolation, still sufficiently predictive and protective, and does the current understanding of environmental chemicals, as derived from these traditional approaches, actually reflect or capture their toxicity in the context of the dynamics of risk factor interactions, be they interactions of chemicals in a mixture context or with other attendant host or intrinsic risk factors? Toxicity may cumulate over the life span at a rate that varies by individual in relation to the actions of other risk increasing or risk mitigating factors that are sustained by that individual. Under realistic environmental conditions, it is not difficult to imagine how insults occurring during development may not be manifest until damage has accumulated sufficiently over time through the addition of or subtraction of toxicity imposed by other existing risk enhancing or mitigating factors, respectively. Unfortunately, many of the studies used for hazard identification, whether based on acute or chronic exposure regimens, typically examine outcomes either at only a single time point or for a very limited duration of the life-span.

To date, attempts to deal with the problem of chemical mixtures has largely been restricted to classes of chemicals that are structurally related. In fact, through the Food Quality Protection Act of 1996, the U.S. EPA was directed to include chemical mixtures in its assessment of risk for pesticides that have a common mode of action. The consequent focus of related efforts has primarily been on organophosphate pesticides. To the extent that structurally-related chemicals share a common target site (acetylcholinesterase for the organophosphates), the consequent effect is often one of additivity for mixtures (Richardson et al., 2001). Such an outcome should hardly be surprising given that the approach may be little different from simply increasing the dose of a representative agent, with saturation of the target site finally occurring at some dose level. Similarly, studies examining effects of

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