

Abstract

Endogenous–Exogenous Chemicals with Neurotoxic Potential [†]

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Introduction: While certain highly reactive chemicals are neurotoxic at high environmental concentrations, low endogenous concentrations of the same substances are required for normal neurophysiological function. **Methods/Results:** The airborne pollutants carbon monoxide, hydrogen sulfide, nitric oxide and cyanide are each employed as endogenous gasotransmitters [1,2], while high concentrations are associated with various neurological disorders. The pyrrole-forming neurotoxic γ -diketone metabolites of certain aliphatic (*n*-hexane) and aromatic solvents (1,2-diethylbenzene) cause axonal polyneuropathy, yet γ -diketones are present in solvent-unexposed subjects, and their urinary pyrrole derivatives increase in diabetes mellitus, a major cause of polyneuropathy [3,4]. Formaldehyde, the common metabolite of two naturally occurring epi/genotoxic neurotoxins (MAM, L-BMAA) linked to a prototypical neurodegenerative disease (Western Pacific Amyotrophic Lateral Sclerosis and Parkinsonism-Dementia Complex) [5], is a neurotoxic and carcinogenic xenobiotic, but the substance is an indispensable component of one-carbon metabolism essential for biosynthetic reactions and epigenetic modulation [6]. Elevated levels of endogenous formaldehyde have been linked to Alzheimer disease [7–9]. **Conclusions:** Such considerations suggest that understanding the relationship between the endogenous functions and effects of such highly reactive chemicals may illuminate both how their endogenous mis-regulation may contribute to neurological disease and the mechanisms underlying their neurotoxic effects from exposure to high concentrations. As taught by Paracelsus (1491–1541), “Poison is in everything, and no thing is without poison. *The dosage makes it either a poison or a remedy*”.



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