Environmental Exposure to Pesticides and Neurodegenerative Diseases

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The effect of environmental contaminants on health is a major concern because over the last two decades, several studies worldwide have shown how chemicals present in our environment can profoundly affect the etiology of some chronic diseases. Indeed, pesticides toxicity has been clearly demonstrated to alter neurological functions and numerous epidemiological studies have shown a relationship between pesticides exposure and the etiology of Parkinson’s disease (PD) [1,2]. However, epidemiological results are inconclusive because there is considerable heterogeneity in results likely due to statistical analysis, methodological differences, study design, control selection, differences in exposure assessment methods and diagnosis of patients.

Recently, there are a tremendous number of studies examining the pathogenesis of PD in animal models exposed to environmental toxins, with an emphasis on pesticides. For this, two pesticides were widely used, the rotenone and the paraquat, because both were associated with PD [3]. Paraquat (1,1’-dimethyl-4,4’-bipyridinum dichloride) was one of the most widely used herbicides in the world due to its low cost and rapid action. In the United States, it is classified under restricted use, whereas in the European Union, it has been forbidden since July 2007.

Numerous animal studies have demonstrated that paraquat can cause neurodegeneration of dopaminergic neurons [4]. Paraquat is a highly toxic quaternary nitrogen herbicide, not readily absorbed from the gastrointestinal tract, and is even more slowly absorbed across the skin. Upon absorption, paraquat accumulates in the lung and the kidney where it exerts its major acute toxicological effects. Paraquat is very poorly metabolized and its metabolism has been reported to occur via demethylation (monomethyl dipyr dine ion) or oxidation (paraquat pyridone ion and paraquat dipyr dine ion) [5,6].

Paraquat can be transported across the blood-brain barrier by the action of a neutral amino acid transporter carrier such as the system L carrier (LAT-1), which normally carries amino acids L-valine and L-phenylalanine, whose administration has been reported to prevent paraquat-induced neurotoxicity [7,8]. Paraquat has been shown to induce proteasome dysfunction and α-synuclein aggregation [9,10]. Furthermore, paraquat has been shown to potentiate α-synuclein-induced toxicity. However, there is still a lot of controversy regarding the neurotoxicological actions of paraquat [11]. Paraquat and most of environmental toxicants are known to induce oxidative stress by the production of reactive oxygen species as byproducts of detoxifying metabolism, alterations in the mitochondrial metabolism or by their own redox cycling properties per se.

The molecular mechanisms induced by pesticides vary according to their chemical structure. For instance, although diquat and paraquat displayed similar chemical structure but the underlying mechanisms are somewhat different. Paraquat and the toxic compound MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) have also similar structure. MPTP crosses the blood-brain barrier and is biotransformed by glial cells to MPP+ (1-methyl-4-phenylpyridinium). MPP+ is taken up by neurons through dopamine transporters and induces neuronal cell death by inhibition of mitochondrial complex I and induction of oxidative stress. However, the role of paraquat on mitochondrial activity is unclear, being only a weak inhibitor of the mitochondria respiratory chain [12]. The inhibition of the dopamine transporters protect against paraquat-induced toxicity [13,14] but the role of dopamine transporters on paraquat-induced neurotoxicity is unclear as it has been shown to be neither a substrate nor inhibitor of dopamine transporters [15,16]. Nevertheless, the study of paraquat’s neurotoxic properties has provided valuable information regarding the potential mechanisms involved in the progression of neurodegeneration associated with environmental toxicity.

Subsequent studies found that the rotenone model accurately recapitulates many other features of PD and is also considered to contribute to the etiology of PD. Rotenone was first used to model PD in 1985 [17]. It has been largely thought that rotenone induces reactive oxygen species by inhibition of the mitochondrial respiratory chain complex I. Although rotenone has widely used in experimental model of neurotoxicity, it lacks significant specificity for the central nervous system. Exposure to the fungicide maneb has been also associated with PD [18,19]. Maneb has been shown to induce oxidative stress, protein carbonylation and α-synuclein aggregation due to proteasomal dysfunction [20]. Both extracellular (microglial) and intracellular oxidases have been suggested to mediate reactive oxygen species formation via redox cycling of maneb [21]. Stimulation of free radical production, induction of lipid peroxidation, and disturbance of the total antioxidant capability are also mechanisms of toxicity of organophosphates (OPs), bipyridyl herbicides and organochlorines [22]. In addition to cholinergic overstimulation, pesticides could also activate glutamatergic neurons leading to the activation of NMDA receptors and further generation of free radicals resulting in neuronal degeneration [23]. Thus, the molecular mechanisms involved in neuronal cell death by pesticides are complex and unclear because a given chemical can have multiple modes of action. Experimental data so far clearly demonstrated that oxidative stress, and reactive oxygen species, both mitochondrial and endoplasmic reticulum stress pathways, redox signalling represent the central mechanism for the toxicological effects of pesticides.

However, most of the studies regarding the molecular mechanisms of pesticides have been investigated in neuronal cell types. Compared to neurons, astrocytes are more resistant to pesticides induced oxidative stress [24].

There is an extensive geographical overlap of different pesticides. Therefore, humans were always exposed to several toxicants and it is clear that a single toxin could not represent the sole environmental risk.
factor for PD. However, the experimental effects of the combination of different pesticides were poorly investigated. For instance, exposure to paraquat with maneb or iron exerts their toxicity by mechanisms involving synergistic processes or the activation of completely different signal transduction pathways. Due to the complexity of the effects of environmental exposures on human health, the synergistic effects of different environmental toxicants should be investigated. Combined effects of different pesticides might be a relevant area of research, which could uncover new mechanisms by which environmental exposures regulate neurodegenerative diseases.

Synergistic effects between environmental exposures and gene interactions might also predispose to sporadic PD. Several studies have demonstrated that sensitivity to chemical exposure varies among individuals. These studies indicate new ways of thinking about disease etiology, showing that disease risk is best predicted by considering genetic and environmental factors in tandem. Pesticides can change gene expression through a broad array of gene regulatory mechanisms. How the environment changes gene expression and how this can lead to disease should be explored. One important mechanism of these chemicals is the alteration of gene expression, mediated by a chronic and low dose of pesticides for decades.

Pesticide toxicity depends on the dopamine transporters genetic variability [25] or GST polymorphisms [26,27]. Therefore, a better prediction of the genetic predisposition in the context of environmental exposures will be crucial for the prevention of chronic diseases. Finally, the monitoring of biomarkers (DNA damage, such as chromosomal aberrations, sister chromatid exchanges...) associated with genetic predisposition on individuals exposed to pesticides should move the field toward a better public health benefit.

Although there is much more to be investigated, the existing knowledge should be considered as soon as possible. A global public health action is required shortly to reduce toxic pesticides exposure to attenuate and to prevent chronic diseases such as neurodegenerative diseases with a long lasting etiology. The effect of pesticides exposure on chronic diseases is an important human health challenge that requires suitable attention among neuroscientists, in conjunction with other scientists. There is an urgent need for experts in the field of pharmacology, neurosciences, clinical, chemistry, agrochemical companies, farmers and members of governmental regulatory agency to work together in the near future.

References