Life Sciences xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Potential role of organochlorine pesticides in the pathogenesis of neurodevelopmental, neurodegenerative, and neurobehavioral disorders: A review

Seyed Soheil Saeedi Saravi [a,b,c], Ahmad Reza Dehpour [a,b,*]

[a] Experimental Medicine Research Center, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[b] Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[c] Department of Toxicology–Pharmacology, Faculty of Pharmacy, Guilan University of Medical Sciences, Rasht, Iran

ARTICLE INFO

Article history:
Received 30 July 2015
Received in revised form 1 November 2015
Accepted 4 November 2015
Available online xxxx

Keywords:
Pesticide
Organochlorine
Neurodevelopmental disorder
Neurodegenerative disorder
Neurobehavioral disorder

ABSTRACT

Organochlorine pesticides (OCPs) are persistent and bioaccumulative environmental contaminants with potential neurotoxic effects. The growing body of evidence has demonstrated that prenatal exposure to organochlorines (OCs) is associated with impairment of neuropsychological development. The hypothesis is consistent with recent studies emphasizing the correlation of environmental as well as genetic factors to the pathophysiology of neurodevelopmental and neurobehavioral defects. It has been suggested that maternal exposure to OCPs results in impaired motor and cognitive development in newborns and infants. Moreover, in utero exposure to these compounds contributes to the etiology of autism. Although impaired neurodevelopment occurs through prenatal exposure to OCs, breastfeeding causes postnatal toxicity in the infants. Parkinson's disease (PD) is another neurological disorder, which has been associated with exposure to OCs, leading to α-synuclein accumulation and depletion of dopaminergic neurons. The study aimed to review the potential association between pre- and post-natal exposure to OCs and impaired neurodevelopmental processes during pregnancy and neuropsychological diseases such as PD, behavioral alterations, seizures and autism.

1. Introduction

1.1. Organochlorine pesticides

Food production capacity is faced with an ever-growing number of challenges, including a world population expected to grow to nearly 10 billion by 2050 and a falling ratio of arable land to population. Based on the evidence, the explosive increase in world population, mostly in developing countries, has exceeded the need for food production [1–3]. Agricultural production has been accompanied by continuous growth in the number and quantity of pesticides for plant and crop protection, leading to intensive development of agrochemicals present in the environment. This is associated with environmental contamination and human health hazards worldwide [2–4].

Pesticides are widely used chemical compounds to kill, repel, or mitigate pests. The conventional pesticides are classified as herbicides, insecticides and fungicides [5,6]. The worldwide consumption of pesticides is estimated over 2.27 billion kg each year for agricultural, residential, commercial or industrial settings [5,6]. Although pesticides are essential in modern agricultural practices, the control of food residues of pesticides is a growing source of concern for the general population due to their biocidal and potential risks. Occupational exposure to pesticides can be dangerous to consumers, workers and close bystanders during manufacture, transport and/or consumption. Particular uncertainty exists regarding the neonatal and/or long-term adverse effects of low-dose pesticide exposures [2,3]. It shows that infants and adolescents are particularly vulnerable to pesticides. However, current surveillance systems are inadequate to characterize potential pesticide-induced diseases [2,7]. The documents have consistent links between exposure to pesticides and serious illnesses such as neurological disorders, cancers, reproductive complications, birth defects, intrauterine growth retardation, and fetal death [8–10].

OCPs are widespread persistent organic pollutants (POP), which includes polychlorinated biphenyls (PCBs), cyclodienes, hexachlorobenzene (HCB), dichlorodiphenyltrichloroethane (DDT), and dichlorodiphenyl dichloroethylene (DDE), a metabolite of DDT [11]. OCs exert their adverse effects through energy metabolism changes, persistent opening of the sodium channels and interaction with gamma-aminobutyric acid (GABA) receptors, resulting in disruption of the sodium/potassium currents of the nerve fibers [12–14]. Although the consumption of OCs has been banned in most of the countries, these compounds can still be detected in the environment, and animal and human tissues [10,15–17]. Epidemiological studies have indicated that the exposure of pregnant mothers to OCPs results in an impaired

* Corresponding author at: Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, P.O. Box: 13145-784, Tehran, Iran.
E-mail addresses: dehpour@yahoo.com, dehpourar@tums.ac.ir (A.R. Dehpour).

http://dx.doi.org/10.1016/j.lfs.2015.11.006
0024-3205/

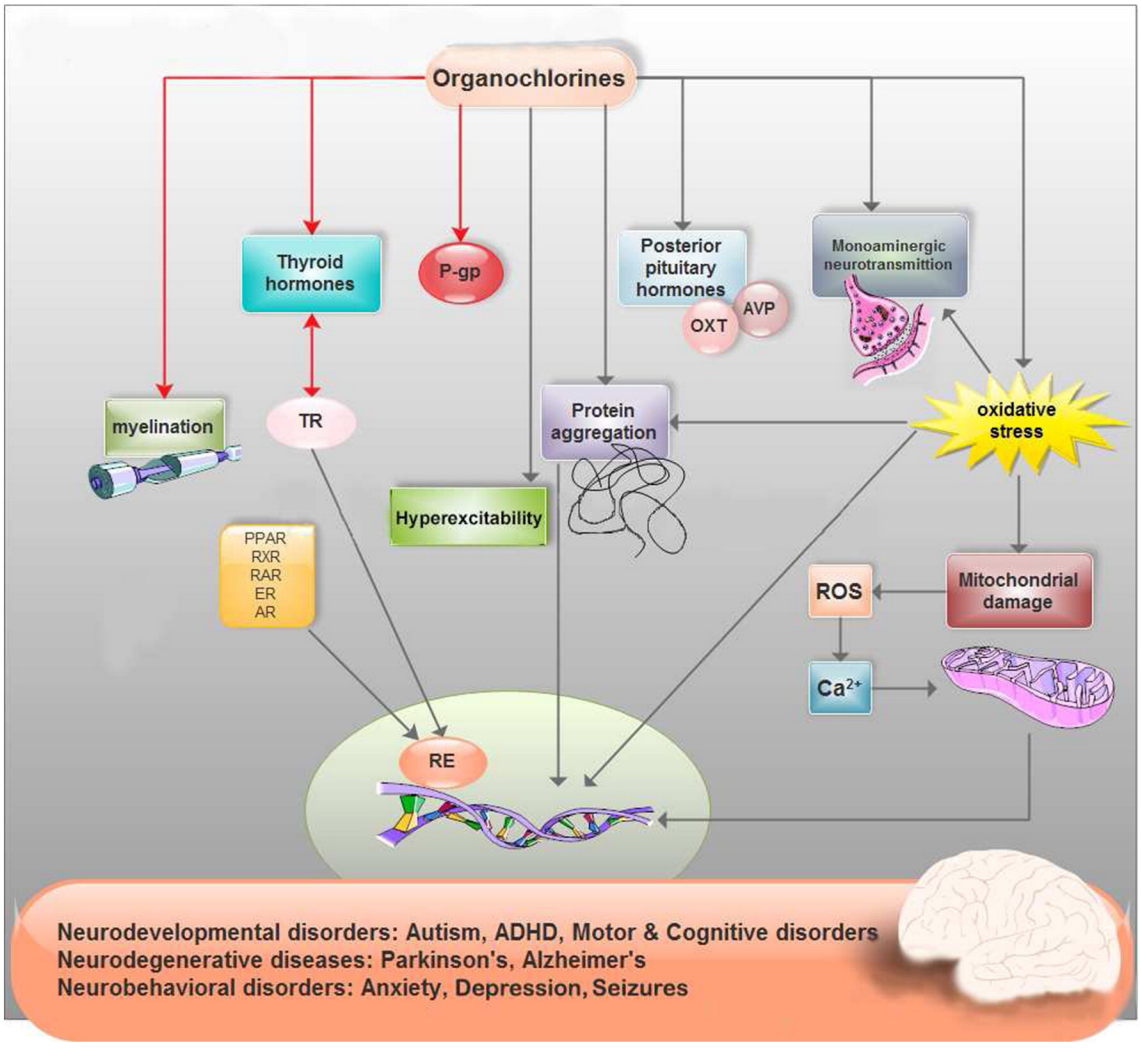

Fig. 1. A schematic model for mechanisms by which organochlorine pesticides induce and develop neurological disorders. ROS: reactive oxygen species, OXT: Oxytocin, AVP: Arginine vasopressin, P-gp: P-glycoprotein, TR: Thyroid receptor, PPAR: Peroxisome proliferator-activated receptor, RXR: Retinoid X receptor, RAR: Retinoic acid receptor, ER: Estrogen receptor, AR: Androgen receptor, RE: response element, ADHD: Attention deficit/hyperactive disorder. Gray arrows: induction, Red arrows: inhibition. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

neurodevelopment and postnatal neuropsychological defects, including poor cognitive development, impaired motor functions, inattention and altered activity, and autism, as well as an increased risk of major chronic diseases such as cancers and endocrine system dysfunction later in life [18–22]. Moreover, commonly used OCPs may have lasting effects on the central and peripheral nervous systems. Growing evidence has indicated that OC exposure is linked to enhanced risk of dementia and Alzheimer's disease (AD) and other neurodegenerative disorders such as PD [23,24].

However, in this comprehensive overview, attempts were made to discuss the association of pre- and postnatal, and long-term exposure of pesticides in adulthood with the incidence of various neurodevelopmental, neurodegenerative, and neuropsychological disorders in neonates, infants and adults, as well as general mechanisms underlying the diseases. In this review, we have provided an overview of OCs-induced neurological disorders and a simple schematic of the underlying mechanisms.

1.2. Human exposure to OCs

Most pesticides are designed to harm or kill pests, but similarity of pests' biological systems to humans can threaten the human health through influencing different human organs and systems. Based on the findings, pesticides can be dangerous to consumers, workers and close bystanders during manufacturing and transportation [2,3,25,26]. Some classes of pesticides cause both external irritation injuries and internal poisoning illnesses. It is worth noting that although the use of OCs has been forbidden in many countries, they are still consumed and remain in the environment and in human tissues [27,28]. The persistence of OCs in the environment and food chain is attributed to their high stability and lipophilicity, and slow rate of elimination from the body. The pesticides are accumulated in the human adipose tissue through the consumption of contaminated food, especially fish and animal fat, which in turn leads to the accumulation and possible toxic effects of OCs [29–31]. The health hazards of OCs depend on the type of pesticide, and level and duration of exposure. [2,3] Consequently, the pesticides enter into the body via four main routes, including dermal, respiratory, oral, and ocular [3].

2. Role of OCs in nervous system disorders (Fig. 1, Table 1)

2.1. OCs and impaired neurodevelopment

The developmental processes of human brain and nervous system begin shortly after fertilization and extend beyond birth [32]. Several studies have shown that OCs, such as DDT, cross the placenta and

Please cite this article as: S.S. Saeedi Saravi, A.R. Dehpour, Potential role of organochlorine pesticides in the pathogenesis of neurodevelopmental, neurodegenerative, and neurobehavioral disorders: A review, Life Sci (2015), http://dx.doi.org/10.1016/j.lfs.2015.11.006