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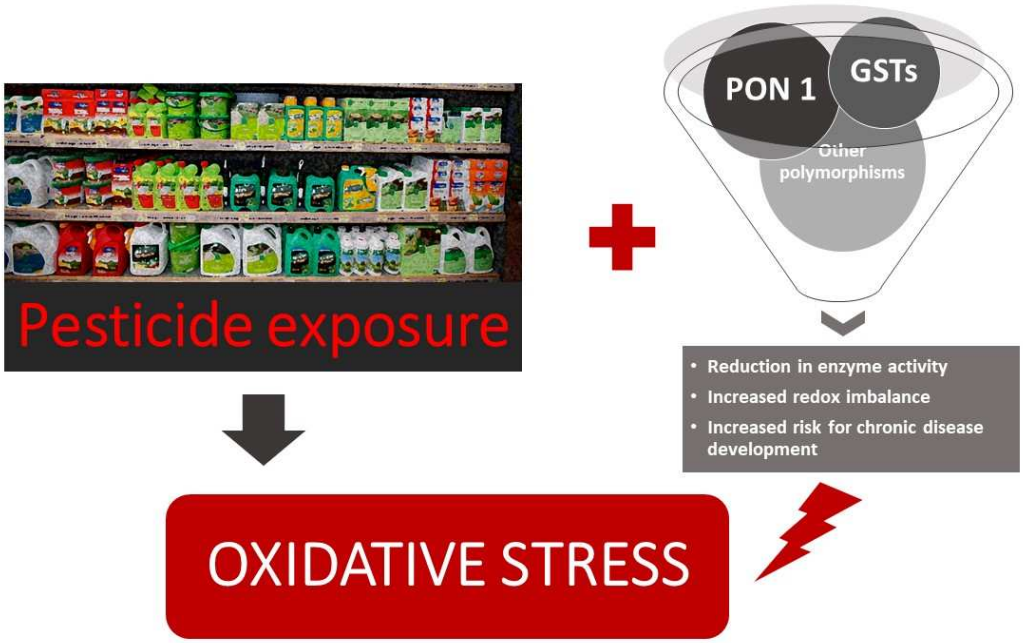

Influence of genetic polymorphism on pesticide-induced oxidative stress

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Abstract

The use of pesticides has become a cornerstone for the productivity of crops and, in general, in agricultural settings. Throughout the years, a large number of diseases, both acute and chronic, have been linked to the exposure to such chemicals. Pesticides include a very large number of compounds, which are able to surely contaminate the environment and the workplace. Due to the variables involved, the assessment of exposure to these substances remains difficult, even in occupational settings.

The pathogenesis of chronic diseases related with pesticide exposure involves various mechanisms, including oxidative stress. The production of free radicals is capable of inducing genomic damage, and this process could be enhanced by the reduction of and individual's antioxidant potential. Several studies have demonstrated that genetic polymorphisms can alter the function of enzymes such as Paraoxonase 1 or Glutathione-S-transferase, which are involved in pesticides metabolisms.

This article reviews the scientific literature, highlighting the potential role of genetic polymorphisms in the enhancement of pesticide-induced-oxidative stress. It seems likely that some workers could be at higher risk of developing diseases because of these genetic conditions which today are not taken into account in health surveillance programs.

Keywords: pesticides, polymorphism, oxidative stress, occupational, chronic diseases

1. Introduction

Pesticide exposure has been linked to a wide range of diseases, including cancer [1][2]. The term “pesticides” is generic and comprehends a large number of compounds, with very different targets, chemical structure, and biological effects [3-6]

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Even though “pesticide exposure” may look like a very unspecific statement, epidemiological studies are often forced to consider pesticide exposure in general, since they are almost invariably used as mixtures. Besides that, small farms don’t usually hold detailed registries about pesticide use and workers often fail to remember the products they were using throughout the years. Exposure to pesticides is often influenced by factors such as the weather, the specific task (sprayer, mixer, harvester etc.), so that the assessment of exposure is often considered one of the main bias in retrospective epidemiological studies.
Nevertheless, several studies have linked exposure to specific pesticides (such as organophosphates) with the development of chronic pathologies like cancer and neurodegenerative diseases. The wide spectrum of diseases potentially linked to pesticide exposure highlights the presence of specific and non-specific pathogenic mechanisms, which include oxidative-stress [7-9].
Animal studies and experimental studies [10-13] have often recognized the role of oxidative stress in processes like aging, neurodegenerative disease, cardiovascular disease, cancer and other pathologies. Oxidative stress results from the inability of the cell to neutralize an excess of oxidative species. This excess can be due to endogenous processes or from the assumption of exogenous chemicals, such as pesticides. Prolonged exposure to oxidative processes can lead to peroxidation of cellular structures such as lipids, proteins or even DNA, resulting in potential mutagenic effects (i.e. DNA strand breaks). Several studies confirmed that pesticide exposure could induce oxidative damage. Furthermore, certain individuals seem to be at a higher risk of pesticide induced oxidative stress because of the presence of genetic polymorphism which influence the metabolism of such xenobiotics. Some of these genetic polymorphism have been widely studied, such as Paraoxonase (PON1, PON2, PON3) or Glutathione-s-transferases (GSTs) and many others are currently being studied. These genetic conditions could, in fact, be a relevant risk factor for the development of acute and chronic pathological conditions.

This article reviews the recent scientific literature regarding the influence of genetic polymorphism on pesticides-induced oxidative damage.

2. Methods

A literature search was performed using PubMed, using no time restriction and "pesticides"[Pharmacological Action] OR "pesticides"[MeSH Terms] OR "pesticides"[All Fields] OR "pesticide"[All Fields]] AND ["oxidative stress"[MeSH Terms] OR ["oxidative"[All Fields] AND "stress"[All Fields]] OR "oxidative stress"[All Fields]] AND ["polymorphism, genetic"[MeSH Terms] OR ["polymorphism"[All Fields] AND "genetic"[All Fields]] OR "genetic polymorphism"[All Fields] OR "polymorphism"[All Fields] as the search terms. The search produced a total of 40 results. A final number of 16 articles were selected for this review for actually focusing the topic. The reference lists of selected articles were further screened for relevance. Additional references were obtained using various combinations of the words “pesticide”, “oxidative stress” and “polymorphysm” on MedLine. Articles published in other language than english were excluded.

3. Discussion

3.1 Paraoxonase Polymorphisms

Paraoxonases are a family of mammalian enzymes with aryldialkylphosphatase activity[14]. Human serum paraoxonase-1 (PON1) is one of the three isoforms of paraoxonase (PON 1, PON2, PON3) with a physiological role related to the hydrolysis of a wide range of lactones, including organophosphate pesticides and other xenobiotics. Synthesized in the liver, PON1 is then released into the blood where it associates with high density lipoproteins (HDL)[15]. PON1, PON2 and PON3 genes are located on the long arm of chromosome 7 [16].PON2 is expressed mainly at a cellular level, while PON1 and PON3 are more commonly found in the blood[17]. All three isophorms of PON seem to counter the atherogenic processes mediated by LDL and could have a role in the antioxidant activity of HDL lipoproteins, especially PON1 [18][19]. PON family enzymes seem to have a role in the LDL/HDL balance among healthy subjects [19],but the impact on the pathogenesis of atherosclerosis is still unclear [20].It is relevant to note that, while all three PON enzymes exhibit antioxidant properties [17], only PON1 is capable of metabolizing toxic metabolites of OPs [21]. Among the factors that could influence PON activity, polymorphisms seem to have a major role towards an increased susceptibility to organophosphates pesticides [22-24]. As a consequence, factors mediating PON1 expression and enzyme activity may play a key role in determining susceptibility to OP exposure and oxidative stress [25].

Studies have shown that exposure to pesticides (especially organophosphates) induces oxidative stress[26][27]. In particular, a study conducted on indoor pesticide sprayers (organophosphates, carbamates, pyrethroids) showed an increase in 8-hydroxydeoxyguanosine (8-OHdG) urinary levels, together with an increase in urinary OP metabolites (dimethyl phosphate and dialkyl phosphates)[26]. 8-OHdG is a derivative of deoxyguanosine and is considered a biomarker of DNA oxidation[28]. In 2007, a study by Lopez et al. [29] evaluated the influence of genetic polymorphisms of PON1 enzyme in a group of 81 pesticide sprayers. These subjects, tested twice during the course of a year, showed lower levels of superoxide dismutase (SOD) and glutathione reductase (GR) compared to the control group. Furthermore, individuals with PON1 polymorphisms showed decreased levels of erythrocyte catalase (CAT) and GR expression, enzymes with protective function against oxidative stress.

A study conducted by Hernandez et al.[30] on workers exposed to various pesticides (mainly: N-methylcarbamates, pyrethroids, dithiocarbamates, neonicotinoids and OPs) observed significant interaction between plasma cholinesterase (BChE) activity and PON_{1192R} allele on CAT, glutathione peroxidase and glucose-6-phosphate dehydrogenase activities. Regarding long-term pesticide exposure, a significant interaction was found between eritrocytic acetylcholinesterase (AChE) and PON_{1192QR} and PON_{1108CC} genotypes on GR and between AChE and PON_{1192RR} on SOD. A subsequent study from the same research group [31] used generalized estimating equations (GEEs) to assess the correlation between occupational exposure to pesticides and PON1 enzyme activity. The authors observed a bimodal pattern for paraoxonase in response to OP pesticide exposure: short term exposure was associated with a decrease in PON activity, while long-term exposure lead to an increase of PON enzyme activity. Interactions between PON regulatory region polymorphisms, BChe activity and the activity of other enzymes such as arylesterase and diazoxonase was highlighted. Furthermore, genetic polymorphism PON1192RR seemed to influence arylesterase activity. These findings, altogether, suggest that genetic polymorphism on PON genes, combined with pesticide exposure, could further affect plasmatic antioxidant potential.

Such evidences are strengthening the hypothesis that genetic polymorphisms could enhance pesticide-induced oxidative damage; recent studies are evaluating the role of such genetic alterations on pathological conditions such as miscarriage [32] and other foetal alterations [25] in women exposed to pesticides or the development of neurodegenerative diseases (i.e. Parkinson's disease)[33][34].

3.2 Glutathione-*S*-transferases [GSTs]

GSTs are a family of enzymes which catalyze the conjugation of endogenous compounds and xenobiotics with the reduced form of glutathione. This process lead to the formation of hydrosoluble molecules which can then be excreted. Pesticides are one of the substrates of GSTs; in particular, GSTs polymorphisms have been investigated in regard to impaired foetal growth caused by organochlorine pesticides (OCp)maternal exposure [35]. OCp have been reported to cause an excess of oxidative stress in different conditions [36] including pregnancy [37]; Sharma et al. [35] focused on the relation between the frequency of polymorphic alleles of GSTM1 and GSTT1 in woman with idiopathic fetal growth restriction (FGR). The results showed that the prevalence ofGSTM1/GSTT1 was almost similar in both cases and controls, while the presence of the GSTM1-/GSTT1-(null) genotype was significantly higher in FGR cases ($p < 0.05$, OR = 6.42). The authors confirmed that OCp exposure could cause conditions like FGR, and highlighted the potential role of polymorphic GST alleles as a further risk factor.

A brazilian study [38] evaluated a large number of genetic polymorphisms (GSTT1, GSTM1, GSTP1, CYP2A6, PON, OGG1, RAD51, XRCC1, and XRCC4) in relation to oxidative stress biomarkers and enzymes activity. The study was conducted on a group of tobacco farmers (exposed group) vs. a smaller group of non-exposed individuals from the same geographic area. The results showed that only GSTM1 null and CYP2A6*9 were associated with cytokinesis-blocked micronuclei assay results.

A case-control study conducted by Bhat et al. [39] aimed to elucidate the relation between GSTs polymorphisms and coronary artery disease (CAD). The authors enrolled 200 cases diagnosed with CAD and an equal number of matched controls, which were tested for GSTT1 and GSTM1 gene polymorphisms via PCR. The results showed a significantly ($p=0.038$) lower frequency of GSTT1 null genotype in patients with CAD compared to controls. Statistical analysis indicated that GSTT1 null genotype was protective against CAD($p=0.028$). On the other hand, GSTM1 null genotype did not seem to influence the pathogenesis of CAD.

3.3 Other genetic polymorphisms

Oxidative stress is often implied as a key component in the development of various forms of disease, especially chronic diseases. Gene-environment interplay has also a very relevant role since genetic characteristics can influence to a great extent the response of an individual to a potentially harmful agent. Gene-environment approach is becoming particularly significant for conditions, such as Parkinson's disease (PD), which aetiology has not yet been fully elucidated. A study from Todorovic et al.[40] used a large Australian cohort (PD cases=1338, controls=1379) to assess the relation between this condition and the NFE2L2 genetic variations.NFE2L2 mediated antioxidant response pathway genes had already been reported to be present in biopsies from the olfactory mucosa of PD patients, in a previous study from the same group [41]. The authors used a haplotype-tagging approach that identified an association between the tagging SNP rs2364725 and PD. After controlling for regular pesticide exposure and smoking habit, the authors found out that the rs2706110 gene variant was significantly related to pesticide use. In conclusion, the results indicated that NFE2L2 polymorphisms could influence both susceptibility and onset of PD.

A recent cross-sectional study [42] evaluated haematological abnormalities, oxidative stress biomarkers and the influence of the quinone oxidoreductase 1 (NQO1) C609T polymorphism in 100 greenhouse workers and 104 controls. Workers exposed to a mixture of pesticides had a significant decrease in erythrocytes and haemoglobin. Oxidative stress indicators were altered among the sprayers: plasma cholinesterase (PChE) and GSH levels were both decreased, while lipid peroxidation (LPO), protein carbonyl, superoxide dismutase activity, and total antioxidant capacity were all significantly increased. Genotoxicity

parameters were significantly related to oxidative stress, although NQO1 C609T polymorphism was not significantly associated with studied biomarkers.

Conclusions

Exposure to pesticides is a major concern both in occupational settings and in the environment. Table 1 shows that many studies have already demonstrated an oxidative stress response to pesticides, while articles examined in this review are quite consistently highlighting that genetic polymorphisms (mainly PON1 and GSST1/GSM1) can further potentiate this phenomenon.

It is worrying to think that workers who carry such genetic alteration could be at higher risk of developing chronic diseases, which onset is often after the end of their working life and of health surveillance programs. More studies are certainly needed in this area to assess the real burden of specific polymorphisms in the development of diseases. Even though this is a controversial topic from an ethical point of view, these alterations could be considered, in the future, an element to be taken into consideration for an individual's suitability to certain jobs.

Table 1. Epidemiological studies linking pesticides exposure and oxidative stress (last 5 years).

Author	Study type	Population	Outcome
V Kahl et al. [43]	Case-control	40 farmers exposed to pesticides vs. 40 non-exposed age and gender matched controls	Dietary intake and genetic susceptibility polymorphisms in MTHFR (rs1801133) and TERT (rs2736100) genes were considered. MTHFR CT/TT genotype influenced nucleoplasmic bridges, nuclear buds, and TL in the exposed group, whereas TERT GT/TT only affected micronucleus frequency. Positive correlation of TL and lipids and an inverse correlation of TL and fibers.
C Lerro et al. [44]	Longitudinal	30 farmers exposed to pesticides [atrazine and 2,4-dichlorophenoxyacetic acid [2,4-D]] vs. 10 non-exposed controls	Urines collected at 5 times of the year (pre-planting, planting, growing, harvest, off-season) measured for Atrazine mercapturate (atrazine metabolite), 2,4-D, and oxidative stress markers (MDA, 8-OHdG, 8-isoPGF). Farmers showed higher urinary atrazine mercapturate and 2,4-D levels. Multivariate analysis showed 2,4-D was associated with elevated levels of 8-OHdG.
V Silva et al. [45]	Case-control	121 tobacco farmers occupationally exposed to pesticides mixtures and nicotine vs. 121 non-exposed controls	PON1 Gln/Gln genotype was associated with increased MN frequency. SOD2 Val/Val showed association with increased frequency of MN and NBUD and decreased antioxidant activity. The XRCC1 Arg/Arg showed protective effect for MN, BN and TL, which was also positively influenced by OGG1 -/Cys. MN were decreased in XRCC4 -/Ile farmers.
MDP Cattelan et al. [46]	Case-control	152 farmers were divided into two groups basing on a questionnaire: 84 pesticide users vs. 68 non-users	Pesticide users showed higher neck circumference and significantly increased markers of oxidative stress, TBARS and carbonyl compounds, as well as significant reduction of antioxidant enzymes SOD, GPx e GSH, and in the dosages of total cholesterol, alkaline phosphatase, albumin, total leukocytes, monocytes and platelets. No mutagenic damage was recorded.
V Kahl et al. [47]	Case-control	56 tobacco farmers exposed to pesticides vs. 74 not exposed individuals	DNA damage was significantly increased in farmers and positively associated with years of exposure. Inverse relationship between DNA damage and total equivalent antioxidant activity was demonstrated for exposed and unexposed groups. Exposed group had a significant reduction in TL. Exposed individuals showed an increase in lipid peroxidation, positively correlated with DNA methylation.
D Lozano-Paniagua et al. [48]	Longitudinal	175 greenhouse workers exposed to insecticides and fungicides vs. 91 non-exposed controls. Two	TBARS, FRAS, SHT,GGT, PON1, AChE were measured in serum. Exposed workers had an increase in oxidative stress, countered by an increase in FRAS, SHT and PON1.

		exposure periods were considered [low and high].	
CHJ Pereira et al. [49]	Case-control	50 rural workers exposed to pesticides vs. 46 controls from the same city and 29 controls from another city	MN, TBARS, CAT and AChE were assessed. Comet assay on peripheral blood lymphocytes of both groups showed significantly higher DNA damage in the exposed group vs controls ($p<0.0001$). MN ($p<0.001$), NBUDs ($p<0.005$) and NPBs ($p<0.0001$) were significantly higher in the exposed group.
R Zepeda-Arce et al. [50]	Cross-sectional	60 subjects with high exposure vs 126 subjects with moderate exposure vs. 22 controls	MDA, SOD, CAT, GPx, GR were assessed as a measure of oxidative stress. Comet assay was used to assess genotoxicity. SOD and CAT activities were higher in high exposure group compared to the control group. MDA levels and GPx activity were positively correlated in moderate exposure group. GR and CAT were positively correlated among high exposed, as well as DNA damage parameters and MDA levels.
KM Lee et al. [51]	Cross-sectional	84 subjects exposed to pesticides	MDA, isoprostane, 8-OHdG and DAP were measured. A correlation analysis was performed for PEI, CEI, DAP and other oxidative stress biomarkers. Oxidative stress biomarkers and pesticide metabolites had a positive correlation. Indicators of oxidative stress was associated with a pesticide metabolite DMP, DEP, and DETP.
L Wang et al. [52]	Case-control	20 farmers exposed to chlorpyrifos vs. 15 controls	Chlorpyrifos exposure was assessed. Urinary 8-OHdG was significantly higher in the exposed group on the first day after chlorpyrifos spraying.
PV Rekhadevi et al.[53]	Case-control	106 female cotton field workers exposed to pesticides vs 106 controls	Comet, micronucleus and chromosomal aberrations tests were carried out in peripheral blood lymphocytes. The results showed an increased frequency of micronuclei, chromosomal aberrations and DNA damage in the exposed group.
F Madani et al. [54]	Case-control	50 farmers exposed to pesticides [mainly: Mancozeb, Metribuzin, Malathion] vs. 60 age matched controls.	Plasmatic vitamin C and E levels and erythrocyte GSH were significantly decreased among the exposed group, as well as CAT and SOD. On the other hand, farmers had increased O_2^- levels and erythrocyte MDA and carbonyl protein content.
AS Gaikwad et al. [55]	Case-control	27 pesticide sprayers vs. 27 controls	Uric acid and MDA were significantly increased in the exposed. MN assay on buccal mucosal cell showed significant number of micronucleated cells among farmers.
Koureas M et al. [56]	Case-control	80 pesticide sprayers vs. 85 rural residents vs. 121 city inhabitants	Pesticide sprayers had significantly higher levels of 8-OHdG compared to controls. Seasonal exposure to neonicotinoid and to glufosinate ammonium showed great impact on 8-OHdG levels.
RK Sharma et al. [57]	Case-control	70 agricultural pesticide sprayers vs 70 controls	SOD, CAT, GST, GPx, AChE, lipid peroxidation and GSH were assessed in blood samples. MDA and antioxidant enzyme activity were increased among the exposed. GSH, RBC-AChE activity and plasma antioxidant potential were markedly

	reduced in farmers. Enhanced mRNA expression of CYP2E1 and GST-pi in WBC was found in the exposed group.

Abbreviations: 8-OHdG, 8-hydroxy-2'-deoxyguanosine; 8-isoPGF, 8-isoprostaglandin-F2α; AChE, acetylcholinesterase; BN, binucleated cells; CAT, catalase; CEI, cumulative exposure index; DAP, dialkyl-phosphate; DEP, diethylphosphate; DETP, diethyl phosphorothioate; DMP, dimethylphosphate; FRAS, ferric reducing ability of serum; GGT, gamma-glutamyl transpeptidase; GPx, glutathione peroxidase; GSH, glutathione; GST-pi, gutathione-S-transferase isoform pi; MDA, malondialdehyde; MN, micronuclei; MTHFR, Methylene tetrahydrofolate reductase; NBUD, nuclear buds; OGG1, 8-Oxoguanine glycosylase; PEI, pesticide exposure month; PON1, paraoxonase-1; RBC, red blood cell; SHT, total thiol groups; SOD, Superoxide dismutase; TBARS, thiobarbituric acid reactive substances; TERT, telomerase reverse transcriptase; TL, telomere length reduction; TTL, telomere length; XRCC1, X-ray repair cross-complementing protein 1.

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