Effects of quercetin on polychlorinated biphenyls-induced liver injury in rats

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Abstract

Introduction: Polychlorinated biphenyls (PCBs), used as pesticides in agriculture, can lead to irreversible injuries in living organisms, particularly in liver. Oxidative stress has been implicated in the liver pathogenesis induced by different molecules, including PCBs. It has been demonstrated that quercetin, an antioxidant flavonoid found in the diet, exhibits a potent antioxidant effect in different liver pathologies.

Objective: To evaluate oxidative stress caused by PCBs in liver and the antioxidant activity of quercetin.

Methodology: We used male Wistar rats (n = 36), divided in 4 groups: control, quercetin (50 mg/kg/day), PCBs (0.4 ml/kg/day), and rats treated with both PCBs and quercetin. On day 25 blood was collected to assess liver integrity (enzymes AST, ALT and ALP), and liver samples to measure oxidative stress (TBARS), activity of antioxidant enzymes (SOD, CAT, GPx) and DNA damage (micronucleus assay), and histological damage.

Results: TBARS concentration and SOD activity were significantly higher in PCBs animals as compared to the PCB group receiving quercetin. CAT and GPx decreased in PCBs and increased when quercetin was added. The histological analysis showed damage to hepatocytes in PCBs, but quercetin was able to afford protection against such damage. The micronucleus test showed there was an increase in the production of microcenum nucleus compared to control, and quercetin was able to reduce this effect.

Conclusion: Contamination with PCBs led to increased lipid peroxidation and DNA damage, and the use of antioxidant quercetin was effective in reducing PCBs-induced liver injury.

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Key words: Hepatic toxicity. Pesticides. Antioxidants.

EFECTO DE LA QUERCETINA SOBRE LA LESIÓN HEPÁTICA INDUCIDA POR BIFENILOS POLICLORADOS EN RATAS

Resumen

Introducción: los bifenilos policlorados (PCBs) son pesticidas ampliamente usados en agricultura que pueden inducir daños irreversibles particularmente en el hígado. El estrés oxidativo ha sido implicado en diversas patogénesis hepáticas, incluidas las relacionadas con PCBs. La quercetina, un flavonóide de la dieta, ha demostrado tener un potente efecto antioxidante en diversos modelos de patología hepática.

Objetivo: Evaluar el estrés oxidativo hepático inducido por PCBs y la actividad antioxidante de la quercetina.

Metodología: Se usaron ratas macho de raza Wistar (n = 36), divididas en cuatro grupos: control, quercetina (50 mg/kg/día), PCBs (0.4 ml/kg/día) y ratas tratadas tanto con PCBs como con quercetina. El estrés oxidativo se evaluó mediante la determinación de las concentraciones de TBARS, la actividad de SOD, CAT y GPx, y la formación de micronúcleos en el ADN.

Resultados: El estrés oxidativo se incrementó en las muestras de PCBs en comparación con las muestras de control. La quercetina fue capaz de revertir estos cambios. La formación de micronúcleos en el ADN aumentó en las muestras de PCBs en comparación con el grupo de control.

Conclusión: La quercetina fue capaz de revertir los daños oxidativos provocados por PCBs.

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Palabras clave: Toxicidad hepática. Pesticidas. Antioxidantes.

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Introduction

Exposure of living organisms to xenobiotic agents, such as polychlorinated biphenyls (PCBs), can facilitate the formation of free radicals. Environmental and nutritional factors interfere with the production of free radicals and thus may lead to a situation of oxidative stress. This has increased environmentalists and researchers’ interest in controlling and/or decreasing factors that may interfere with the environment. Polychlorinated biphenyls are a class of synthetic organochlorine compounds that have been used in industry since 1930. Because of their physical properties—resistance to high temperatures and electrical currents—PCBs are used as dielectric fluids in capacitors and transformers. Environmental contamination with PCBs occurs through handling accidents, vapors inhalation, inadequate storage, and leakage of residues reaching sewers, rivers, lakes and oceans. Animals feeding on contaminated grass and water end up accumulating PCBs residues. These have high affinity for lipids, and because of toxicity and great persistence of these compounds in the human body, they are passed on over generations, i.e., from mother to children during gestation. PCBs and other organochlorine pesticides have cumulative effects in the organisms, particularly in humans.

Oxidative stress (OS) occurs in living organisms when the production of free radicals surpasses the ability of antioxidant defense systems to remove them. OS is thus characterized by an increase in free radicals or a decrease in antioxidant defenses eventually leading to damage to cell structures, such as lipoperoxidation and oxidation of proteins, enzymes, carbohydrates and deoxyribonucleic acid (DNA), resulting in functional changes and damage to vital functions in several tissues and organs.

Free radicals in the organism are quenched by the antioxidant system, which can be endogenous (enzymatic or non-enzymatic) and exogenous. Enzymatic antioxidants include superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), and non-enzymatic antioxidants are glutathione (GSH), histidine peptides, iron-binding proteins (transferrin and ferritin) and CoQH. The exogenous antioxidants are, those obtained from the diet, with the organism using different substances such as tocopherol (vitamin E), β-carotene (provitamin A), ascorbic acid (vitamin C) and the phenolic compounds, such as flavonoids. Quercetin (Q) is a major flavonoid whose chemical composition allows it to sequester free radicals and chelate metal ions, reported to have an excellent antioxidant response against OS.

This work was designed to evaluate liver injury caused by PCBs in rats by assessing lipoperoxidation, antioxidant enzyme levels and DNA damage, as well as the potential of antioxidant quercetin to protect against these deleterious PCB-induced changes.

Materials and methods

Animals

Thirty-six male Wistar rats weighing 170g were used. They were divided in four groups: control (CO), quercetin (Q), polychlorinated biphenyls (PCBs), and polychlorinated biphenyls plus quercetin (PCBs+Q). The animals were kept in the vivarium of the Lutheran University of Brazil (ULBRA) on a 12 hours light/dark cycle and room temperature at 20-25°C. Water and food were given ad libitum. Animals received PCBs by gavage and quercetin intraperitoneal (i.p). After treatment with PCBs and Q, animals were anesthetized with xylazine hydrochloride 50 mg/kg and ketamine hydrochloride 100 mg/kg body weight i.p to remove the liver, spleen, and femur. Through a heparinized capillary, a blood sample was taken from the retro-orbital plexus. This was followed by euthanasia with exsanguination under anesthesia.

For oxidative stress assessment, organs and blood were collected and assayed in the Laboratory of Oxidative Stress and Antioxidants of the Universidade Luterana do Brasil (ULBRA), Canoas, Brazil. For toxicological analyses, collected organs were stored in appropriate glass flasks and transferred to their laboratories and frozen at -20°C until assayed. Experiments followed a protocol approved by the Animal Ethics Committee of the Lutheran University of Brazil (ULBRA) with the recommendations of the European Union regarding animal experimentation.

PCBs doses were determined by the Laboratory of Persistent Pesticides Analysis (LAPP) of the Universidade Federal de Santa Maria (UFSM) (with approval
by the Ethics Committee of UFSM). From these individual solutions we performed contamination of rats of 10 mg L⁻¹ of each PCB type, as described in the Normative Instruction # 24 of August 2011 of the Brazilian Ministry of Agriculture⁹, Livestock and Food Supply, Agriculture Defense Department, reference range of PCBs summation of item (i). The dose was calculated by the LAPP as 0.4 mL of the above-mentioned solution per kg/animal weight.

**AST, ALT and ALP determination**

A enzymatic commercial kit (Boehringer Mannheim, Germany) was used for AST and ALT determination in plasma through kinetic measurement at 567 nm. An automated enzymatic method was used to determine plasma ALP activity. We used the para-nitro-phenyl-phosphate substrate plus water, which forms para-nitrophenol, a highly intense yellow compound with maximum absorbance of 400 nm.

**Histological analysis**

For histological examination, liver portions were placed in buffered formalin. Later they were included in paraffin blocks, and subsequently cut into 3-µm slices using a microtome. Tissue slices were then stained with hematoxylin-eosin (HE) for standard histological examination. A Labophot Nikon binocular microscope at a magnification of 200x was used.

**Liver homogenates**

Livers were weighed and homogenized for 30 seconds in an Ultra-Turrax (Ika-Werk) for 40 seconds at 4°C in the presence of 1.15% KCl (9 mL per gram of tissue) and methyl phenyl sulfonyl fluoride (PMSF) at a concentration of 100 mM in isopropanol (10 µL per mL of KCl added). Then the homogenates were centrifuged for 10 minutes at 3000 rpm in a refrigerated centrifuge (Sorvall Super T21, Condensed Operating Kendro Laboratory Products, USA). The supernatant was pipetted into Eppendorf flasks, and the precipitate was discarded. The samples were stored again at - 80°C for posterior analyses¹⁰.

**Protein**

We used the Bradford method to quantify protein, with bovine albumin as the standard (Sigma). The samples were measured spectrophotometrically at 595 nm, and values expressed in mg/mL were used to calculate TBARS (thiobarbituric acid-reactive substances) values and antioxidant enzymes¹¹.

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**Lipid peroxidation**

The amount of aldehydes generated by lipid peroxidation is measured by the TBARS method, which measures the amount of substances reacting with thiobarbituric acid. The samples were incubated at 100°C for 30 minutes after addition of 500 µL of 0.37% thiobarbituric acid in 15% trichloroacetic acid and centrifuged at 3,000 rpm (1612.8 × g) for 10 minutes at 4°C. Absorbance was determined spectrophotometrically at 535 nm¹².

**Antioxidants enzyme analyses**

The analysis of superoxide dismutase (SOD) in liver is based on the inhibition of the reaction of the superoxide radical with adrenaline, values expressed in U/mgprot¹³. Glutathione peroxidase (GPx) activity is based on the consumption of NADPH in the reduction of oxidized glutathione and values were expressed in nmol/mgprot. The analysis of catalase (CAT) activity is based on measuring the decrease in hydrogen peroxide, values expressed in pmol/mg prot¹⁴.

**Micronucleus assay**

The micronucleus assay was performed according to the US Environmental Protection Agency Gene-Tox Program¹⁵. The bone marrow was extracted from the two femurs. Smears were prepared directly on slides with bone marrow and blood, two per animal and per tissue. Bone marrow smear was prepared with a drop of fetal calf serum. The slides were stained with 5% Giemsa, air dried and coded for blind analysis. To avoid false negative results and as a measure of toxicity in bone marrow, the ratio of polychromat bands to normochromatic erythrocytes (PCE/NCE) was scored in 1,000 cells. The incidence of micronuclei (MN) was observed in 2,000 PCE for each animal (ie. 1,000 from each of the two slides prepared from the duplicate), using bright-field optical microscopy under 200-1000x magnification. All sides were coded for blind analysis. The test groups were compared to the respective negative controls for gender, separately and in combination.

**Results**

Liver integrity was assessed by determining activity of aminotransferases: aspartate aminotransferase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP). The analysis of liver enzymes (table I) in plasma showed a significant increase in all enzymes in the PCBs group as compared to the other groups. AST was increased by 1,042% in PCBs as compared to CO, and was decreased by 88% in PCBS+Q as...
EFFECTS Interacción 30/04/14 09:56 Página 1144

Cléia Rocha de Oliveira et al.

63% decrease in PCBs+Q as compared to PCBs. A 220% increase in the PCBs as compared to CO and a decrease of 40% in PCBs+Q as compared to PCBs. ALP had a 302% increase as compared to CO and in PCBs+Q it was decreased by 32% as compared to PCBs. ALP had a 230% increase as compared to CO e Q. p < 0.001. Significant difference as compared to CO, Q and PCBs+Q. p < 0.001. **Significant difference as compared to CO e Q. p < 0.001.

The results appear as means ± standard error. CO: Control. Q: Quercetin. PCBs: polychlorinated biphenyls. PXBs+Q: polychlorinated biphenyls quercetin (n = 36). *Significant difference as compared to CO, Q and PCBs+Q. p < 0.001. **Significant difference as compared to CO e Q. p < 0.001.

compared to PCBs, thus showing a potentially beneficial effect of quercetin in different tissues. ALT had a 302% increase as compared to CO and in PCBs+Q it was decreased by 32% as compared to PCBs. ALP had a 220% increase in the PCBs as compared to CO and a 63% decrease in PCBs+Q as compared to PCBs.

Figure 1 shows the results of lipoperoxidation analysis. TBARS concentration was significantly increased by 65% in PCBs as compared to CO, and significantly decreased by 35% in PCBs+Q as compared to PCBs. No significant difference was found in TBARS levels in Q as compared to CO and PCBs+Q (fig. 1A).

SOD was increased by 23% in PCBs as compared to CO, and was decreased by 18% in PCBs+Q as compared to PCBs. Groups CO, Q and PCBs+Q did not show significant differences between each other, which demonstrates antioxidant action of quercetin in PCBs+Q (fig. 1B). Evaluation of CAT and GPx showed a 30% decrease of CAT in Q as compared to CO and a decrease of 40% in PCBs, while GPx activity decreased by 54% in PCBs+Q in relation to its controls. However, PCBs+Q showed a significant increase of both enzymes (p < 0.05. Figures 1C and 1 D).

Through hematoxylin-eosin (HE) staining, we found that CO and Q (fig. 2-A and B), had normal hepatocytes, with well-preserved cytoplasm and nucleus. In PCBs (fig. 2-C), there was evidence of disorganization of hepatocyte cords, inflammatory infiltrate (arrow 1) and necrosis (arrow 2). In PCBs+Q (fig. 2-D), note the reorganization of hepatocyte cords and normal aspect of the tissue.

The micronucleus assay (MN) showed (fig. 3) that PCBs had a 300% increase in the formation of micronuclei as compared to CO, with p < 0.001.

Discussion

Exposure of organisms to xenobiotics can cause cumulative, often irreversible, injuries in human beings.

Polychlorinated biphenyls are used as pesticides for growth of grains and pastures in the animal feeding chain, and accidental exposure to these chemicals may lead to serious, often irreversible, damage to tissues. Morhet et al. found that the toxic effect of PCBs is related to their having great affinity for fat, thus accumulating in adipose tissue in humans and animals. The main form of contamination in humans is, therefore, ingestion of contaminated food, especially those of animal origin.

Although all cell components are susceptible to the action of reactive oxygen species (ROS), which arise from toxic agents, the plasmatic membrane is one of the most affected sites because of lipid peroxidation, which leads to changes in the structure and permeability of cell membranes. As a result, there is a loss of selectivity in ion exchange, release of the content of organelles, such as hydrolytic enzymes of lysosomes, formation of cytotoxic products, such as malondialdehyde, culminating in cell death. Lipoperoxidation can be associated with mechanisms of toxicity exacerbation by xenobiotics, with the aging process and with oncogenesis.

Liver enzymes (ALT, AST and ALP) are markers of hepatic injury, and an increase in their levels suggest liver dysfunction, which may be related to damage to hepatic tissue or even alterations in cell permeability. An increased level of AST, however, is the result of enzymatic degradation not only of hepatic but also of other tissues, such as musculoskeletal tissue damage resulting from heavy physical exercise, myopathy, and hypothyroidism. On the other hand, enzyme ALT is specific to hepatic injuries, like those from steatosis and chronic viral and autoimmune hepatitis. ALP signals to cholestasis present in hepatobiliary disorders arising from intra- or extra-hepatic biliary obstruction, drug-induced cholestasis, biliary cirrhosis, primary sclerosing cholangitis and infiltrative disorders.

In this study, animals that received PCBs showed increased ALT, AST and ALP levels as compared to the other groups, suggesting serious injury caused by PCBs at the dose authorized by the Ministry of Agriculture of Brazil, which considers acceptable a level of 10 mg L⁻¹ of each PCB type, as described in Normative Instruction # 24 of Aug 2011, determined by the Brazilian Ministry of Agriculture, Livestock and Food Supply, Agriculture Defense Department, reference range of PCBs summation of item (i). The dose was calculated in LAPP, with administration of 0.4 mL of the above-mentioned solution per day per kg of animal weight. Concomitant treatment with quercetin for 25 days reduced the hepatic injury caused by PCBs, as demonstrated by the reduced levels of liver enzymes ALT, AST e ALP, evidencing a protective effect by scavenging free radicals, confirmed by reduced lipoperoxidation.

In a trial with rats receiving xenobiotic TAA (liver damage inducer), De David et al. observed an increase in ALT and AST, and upon treatment with
antioxidant quercetin for 4 days the animals presented a decrease in the levels of these enzymes, corroborating the data presented here. In a study by Bona et al.19, liver cirrhosis was induced with carbon tetrachloride (CCl 4), and there was a significant increase in enzymes ALT, AST and ALP and a significant reduction following quercetin treatment. These results corroborate our findings and show the protective effect of quercetin in liver tissue. Using dimetylnitrosamine (DMN), Lee et al.20, showed that quercetin has a hepatoprotective and anti-fibrinogen action. In their study, daily oral administration of quercetin (10 mg/kg) for 4 weeks prevented loss of body and liver weight and preserved ALT and AST levels. This study is in agreement with our results, in which quercetin significantly reduced ALT and AST levels in the PCBs+Q group as compared with PCBs.

The increase in TBARS values suggests that PCBs are able to change membrane lipids, leading to impairment of normal functioning of the cell. This was also reported in other studies with rats by Kang et al.21, in which oxidative overload increased lipoperoxidation in the toxicity induced by thioacetamide (TAA) and in many other studies in which a xenobiotic led to increased lipoperoxidation (De David et al.18, Bona et al.19). In this study, animals receiving antioxidant quercetin concomitantly with PCBs showed decreased lipoperoxidation as evidenced by TBARS, which confirms the findings of other authors.

Because it has several hydroxyls, quercetin is considered a polyphenol, reacting with free radicals formed in the lipid peroxidation processes to become a non-injurious radical. Besides disrupting lipid propagation, it increases GSH levels, which can convert hydrogen peroxide and organics to water and oxygen, preventing formation of hydroxyl radicals, the most injurious free radicals. Quercetin “sweeps” free radicals off and thereby reduces the oxidative and cyto-

Fig. 1.—A: Lipoperoxidation evaluation through the technique of thiobarbituric acid reactive substances (TBARS) (nmol/mg prot) (*Significant increase in lipoperoxidation in PCBs in relation to CO (p < 0.001), Q (p < 0.001) and PCBs+Q (p < 0.05). B: Activity of antioxidant enzyme superoxide dismutase (SOD) (USOD/mg prot), (*Significant difference of PCBs from CO, Q and PCBs+Q (p < 0.05). C: Activity of catalase (CAT), (nmol/mg prot), (*Significant difference of CO from Q, PCBs and PCBs+Q (p < 0.05). D: Activity of glutathione peroxidase (GPx) (nmol/min/mg prot), (*Significant difference of PCBs from CO, Q and PCBs+Q (p < 0.001). (CO = Control, Q = Quercetin, PCBs = polychlorinated biphenyls; PCBs+Q polychlorinated biphenyls plus quercetin). Data appear as means ± standard error of mean. (n = 36).
toxic effect of low density proteins. So, quercetin can inhibit the process of formation of free radicals in three different stages: initiation (by interacting with superoxide anions), formation of hydroxyl radicals (by chelating iron ions) and lipoperoxidation (by reacting with peroxide radicals of lipids).22 SOD increase may be a result from dismutation of superoxide anion due to OS increase23,24. Here we found a significant increase in SOD activity in the PCBs group, which demonstrates activation of a compensatory mechanism through the xenobiotic on cells, in an attempt to decrease the effects induced by the increase in superoxide anion caused by the stress-inducing xenobiotic. The extent of this effect depends on the “aggressiveness” and dose of
the stressor. Similar results were reported in another study in which hepatic toxicity was induced by organophosphate Clorpirifós, an insecticide used in agricultural crops. Quercetin appears to be protective, for SOD was decreased in the PCBs+Q, as reported by De David et al. using TAA and quercetin.

CAT and GPX were reduced in the PCBs groups as compared to the control group, while treatment with quercetin increased both enzymatic activities (p < 0.05). Glutathione peroxidase is mainly responsible for degrading organic peroxides resulting from lipoperoxidation. The use of quercetin was able to significantly increase the activity of this enzyme, suggesting protection through glutathione, thus affording potential protection to the liver in these animals (PCBs+Q).

In the histological analysis of the hepatic tissue using HE, the CO and Q groups showed liver cells organized in hepatocyte chords with normal aspect, clear nuclei and no inflammatory infiltrates. In PCB-exposed animals, however, significant changes were observed: disarrayed hepatocyte chords, presence of inflammatory infiltrates and hepatic necrosis. These findings are consistent with several studies performed by different authors, such as, using other xenobiotics. Quercetin seems to prevent significantly the toxicity of PCBs, preserving the hepatic tissue, with a reorganization of the hepatic parenchyma, accompanied by the return of antioxidant enzyme activity to those of the control group, and a reduction of TBARS levels. Similar results were obtained by Tieppo, in a model with common biliary duct ligation to induce secondary biliary cirrhosis, regenerative nodules, fibrosis and necrotic foci and subsequently treat with antioxidant quercetin, which promoted reduction of hepatic alterations. Other authors also corroborate our results, as well as that quercetin and other antioxidants such as N-acetylcysteine and rutin promoted reduction of hepatic fibrosis. Caffeine and catechins contained in green tea may have a thermogenic effect favoring weight and body fat loss. The use of green tea (catechins and caffeine) showed contradictory results in a meta-analysis for loss and weight maintenance and reduction of fat mass.

Damage to DNA can result from endogenous processes such as errors in DNA duplication, chemical instability in certain DNA bases, or from interactions with exogenous agents such as ionizing and ultraviolet radiation, chemical and biological agents, such as viruses. In our study, the evaluation of micronucleus suggests a genotoxic effect of polychlorinated biphenyls. In evaluating damage to DNA through the micronucleus assay, we found an increase in the formation of MN in the group receiving PCBs, and a decrease in the group treated with quercetin (PCBs+Q), suggesting protection of flavonoid quercetin. Administered PCBs led to the formation of chromosomal fragments which may be due to a clastogenic effect (acentric fragments) or to an aneugenic effect (whole chromosomes), which determines that these chromosomal fragments will not complete the anaphasic migration of cell division, which characterizes the genotoxic potential of PCBs. It is recognized that 35% of malignant tumors are associated with dietary factors, and would be preventable through proper diet and nutrition. Some authors highlight the important role of dietary patterns (meats, fats) in the etiology of several cancers.

Quercetin administration caused a 58% decrease of micronuclei as compared to the PCBs group, which demonstrates greater stability to DNA molecules, preventing the formation of micronuclei, even upon exposure to PCBs, acting as a significant antioxidant in this experimental model. PCBs seem to pose risks to both the environment and humans through contaminated food. Studies by Larramendy et al. on pesticide effects using vertebrate cells in vitro and in vivo also showed induced DNA damage through micronucleus assay, suggesting a genotoxic and/or cytotoxic effect due to their formulation with active ingredients of agrochemicals.

The flavonoid quercetin is able to react with reactive oxygen species, decreasing oxidative damage to DNA, with less DNA oxidation, leading to prevention of tumorogenic processes. In recent studies with Caco-2 cells (colorectal adenocarcinoma), low doses of quercetin led to reduction of DNA breaks. These authors also observed that low concentrations of quercetin induced expression of 8-Oxoguanine DNA glycosylase (hOGG1). HOGG1 is an enzyme involved in DNA repair, and low concentrations of the flavonoid prevent damage and increases DNA repair.

Upon these considerations, we suggest that damage to animal liver induced by PBCs is associated with OS by increasing free radicals or reducing endogenous antioxidant defenses. Use of quercetin at the dose here tested can be effective in minimizing oxidative damage and protecting DNA.

References