Pesticide level in chronic kidney disease patients: a single center study in Shanghai

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Research Article

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Abstract

This study was designed to investigating pesticide burden in Chinese Chronic Kidney Disease (CKD) patients having established etiology and find out the relationship between pesticide and CKD. We tested blood levels of pesticide in CKD patients due to glomerulonephritis (GN) or diabetic nephropathy (DN). Health controls were from physical examination center. Blood pesticides were analyzed by gas chromatography. The result showed the most common pesticide detectable in both CKD group and healthy controls were p, p'-DDE. The positive rate of blood p, p'-DDE was 55.5% in CKD group and 14.3% in healthy control group, with significant difference (c^2=24.383, p 0.01). The blood level of p, p'-DDE (median 2.4ng/ml, range 40.7ng/ml) in DN subgroup was significantly higher (p 0.05) in comparison with GN subgroup (median 0.7ng/ml, range 17.2ng/ml). Blood p, p'-DDE showed significant negative correlation with eGFR (p=0.003, r=-0.263) and positive correlation with 24-hour urinary protein (p=0.013, r=0.22). Binary logistic regression showed p, p'-DDE OR=3.211 95% CI 1.708-6.034 had a significant association with CKD, adjusting for age and Diabetes.

Introduction

CKD is a global public health problem with high incidence. Despite advances in proteomics, genomics and metabolomics, there remains a lack of safe and effective strategies to stabilize renal function in patients with CKD. Consequently, modifiable risk factors that are associated with a progressive decline in kidney function need to be identified. Numerous reports have documented the impact of environmental pollutants on kidney diseases in recent years, and pesticide is one of them Babich, et al. 2020;Kataria, et al. 2015 . Recent studies Ghosh, et al. 2017;Jayasumana, et al. 2015;Lebov, et al. 2016;Shearer, et al. 2021;Wan, et al. 2021 reported a positive association between one or more pesticide exposure and different markers of CKD, suggesting pesticide chronic exposure may increase the risk of ESRD or CKD especially CKD of unknown etiology (CKDu). An observational study by Jayasinghe et al. Jayasinghe, et al. 2018 showed high blood levels of p, p'-DDE which is the most important metabolite of Dichlorodiphenyltrichloroethane (DDT) have a significant correlation with decrease of glomerular filtration rate (GFR) during 10 years. In a present study by Rajapaksha et al. investigated the interaction of pesticides and their metabolites with vital renal enzymes, using molecular docking studies, revealing that pesticides can be a possible high-risk factor towards CKDu.

Above all, there are many evidences suggesting that pesticide may associated with CKD but most studies focus on CKDu as the study population were mostly from CKDu popular region such as Central America, Sri Lanka, India. In our study, we detected blood pesticides of patients having established etiology such as glomerulonephritis and diabetic nephropathy to explore the correlation between blood pesticide and CKD with known etiology.

Method

Study design

A single-center case-control study was conducted at Ruijin Hospital north district, Shanghai Jiaotong University School of Medicine. We recruited 128 patients of CKD with a certain etiology of glomerulonephritis or diabetic nephrology administered during January 2017 and January 2018 in the department of nephrology. Healthy controls were recruited from adults who underwent physical examinations during a health check-up at our hospital and excluded those with kidney disease according to medical history, urinary routine, renal function and urinary

ultrasound. Subjects occupationally exposed to pesticides were excluded. The study was approved by the Institutional Ethics Committee for Human Research (IEC-HR) of Ruijin hospital.

data collection.

Clinical information of patients from CKD group was collected, including: (1) demographic data: gender, age, weight, height, and body mass index (BMI)；(2) complications: hypertension, diabetes, etc. (3) laboratory results: 24-hour urinary protein, plasma albumin, serum creatinine, serum uric acid, estimated glomerular filtration rate, total cholesterol, total triglyceride, hemoglobin； (4) Renal histopathology were collected if the patients had undergone a renal biopsy. The information of gender, age, fasting blood sugar, glycosylated hemoglobin, total cholesterol, total triglyceride, and blood pesticide were collected in healthy controls.

Blood Samples collection and pesticides detection

Venous blood samples (5mL) were drawn after overnight fasting and collected in sterile EDTAcontaining vials. After sampling, 3 mL of blood was sent to the laboratory center of this hospital and 2 ml of whole blood was used for pesticide extraction. Analyses of pesticides were performed using gas chromatography coupled to high-resolution mass spectrometry (GC/HRMS) system.

We tested 26 types of pesticides or metabolites including: α-Hexachlorocyclohexane, β-Hexachlorocyclohexane, Lindane, δ-Hexachlorocyclohexane, Fenitrothion, beta-Endosulfan, p,p'-DDE, buprofezin, alpha-endosulfan, p,p'-DDD, p,p'-DDT, o,p'-DDT, bifenthrin, fenpropathrin, cyhalothrin-1, cyhalothrin-2, cis-permethrin, trans-permethrin, cypermethrin-1, cypermethrin-2, cypermethrin-3, cypermethrin-4, flucythrinate-1, flucythrinate-2, Deltamethrin-1, Deltamethrin-2.

Grading of renal tubulointerstitial lesions

Renal tubulointerstitial lesions were graded according to the degree of inflammatory cell infiltration, tubular atrophy and interstitial fibrosis:

Level 0 (No): Normal, no changes in renal tubules, no or very few inflammatory cells in the interstitium, no fibrosis.

Level 1 (Light): Renal tubular epithelial cells showed mild atrophy, degeneration, focal distribution, a small amount of inflammatory cell infiltration, small focus of fibrosis, lesion range was less than 25%.

Level 2（Medium）: Renal tubular epithelial cells showed moderate atrophy, degeneration and moderate inflammatory cell infiltration, fibrosis, lesions range was 26-50%.

Level 3（Heavy）: Renal tubular epithelial cells showed severe atrophy, degeneration, necrosis, patchy distribution, a large number of inflammatory cells infiltration and fibrosis, the lesion range was more than 50%.

Statistical analysis

Statistical analysis was carried out using SPSS software version 17.0. Normally distributed data were expressed as mean ± SD and non-normal distributed data were expressed by median and interquartile range. Differences between groups were evaluated using the Mann–Whitney U test (where the data were not distributed normally) or Student t test/ANOVA for normally distributed data. The comparison of rates between groups was carried out by

chi-square test. Association of p, p’-DDE with eGFR and 24-hour urinary protein were tested using Spearmen’s correlation analysis. binary logistic regression analysis was used to calculate the risk of CKD.

Results

Demographic and clinical data

The present study was carried out using two groups of study subjects, namely CKD patients and healthy controls. Demographic data of the two groups are shown in Table 1. It can be observed that the study groups were similar in age and gender. Among the CKD patients, 38.3%, 29.7%, 25.8% were in stage 1, stage 2, stage 3, respectively, and 4.7% were stage 4 or 5. We divided CKD group into glomerulonephritis (GN) subgroup and diabetic nephropathy (DN) group according to the etiology, and the clinical data of the subgroups are shown in Table 2. It is presented that patients from DN subgroup were older and had higher BMI, higher 24-h urinary protein (24-h UP), higher blood pressure, lower eGFR, lower hemoglobin than patients from GN subgroup.

Blood levels of pesticides

The most common pesticide detectable in both CKD group and healthy controls were p, p’-DDE, whereas beta-BHC and fenvalerate-1 were detectable in a very small number of subjects in CKD group, and the other 23 pesticides were negative in either group. The positive rate of blood p, p'-DDE was 55.5% in CKD group and 14.3% in healthy control group, with significant difference (c^2=24.383, p□0.01). The blood level of p, p'-DDE (median 0.85ng/ml, range 40.7ng/ml) in CKD group was significantly higher (p□0.01) compared with healthy controls (median 0ng/ml, range 1.7ng/ml). The blood level of p, p'-DDE (median 2.4ng/ml, range 40.7ng/ml) in DN subgroup was significantly higher (p□0.05) in comparison with GN subgroup (median 0.7ng/ml, range 17.2ng/ml).

Clinical characteristics in different levels of blood p, p’-DDE

The blood concentration of p, p’-DDE was divided into three levels using the second and third quartile of CKD group as cutoff points, and we compared the clinical features in different levels. The results were presented in table 3. It can be observed that gender, BMI, Albumin, Hemoglobin, and proportion of DM were similar among subjects with different levels of blood p, p’-DDE, and patients with high concentration of p, p’-DDE (L3≥3.7ng/ml) were older and had lower eGFR, higher proportion of hypertension in comparison with lower concentration groups (L1 and L2). There was similar 24-h UP in L1 and L2, but significantly higher 24-h UP in L3 than L1.

Correlation of eGFR and 24-h urinary protein with blood p, p’-DDE in CKD patients

Correlation analysis of eGFR and 24-h UP with blood p, p’-DDE level is presented in Table 4. Blood p, p’-DDE showed significant negative correlation with eGFR and positive correlation with 24-h UP. However, the sizes of correlation were small, since coefficients of correlation (r) was -0.263 and 0.22, respectively.

Logistic regression analysis for association of p, p’-DDE with CKD

Binary logistic regression analysis was applied to find out the association of blood level of p, p’-DDE with CKD. The result was presented as odds ratio and 95% CI in table 5, and p, p’-DDE□OR=3.211□95% CI 1.708-6.034□showed significant association with CKD, adjusting for age and diabetes.

Blood p, p’-DDE and histopathology of chronic glomerulonephritis

To investigate whether blood p, p’-DDE have a link with the type or severity of renal lesions, we analyzed 87 cases of glomerulonephritis who underwent renal biopsy in our study. The top three pathological types were IgA nephropathy (n=37), membranous nephropathy (MN, n=30), and focal segmental sclerosing nephritis (n=11), so we compared p, p’-DDE concentrations of them, and Nonparametric Kruskal-Wallis H test showed there was no significant difference in blood p, p’-DDE among different types of glomerulonephritis (p=0.123). We analyzed blood p, p’-DDE levels of MN patients with different severity of interstitial lesions. The result was presented in table 6, and the severity of interstitial lesions showed a positive correlation with blood p, p-DDE levels using spearman correlation analysis (p=0.027, r=0.41). In IgA nephropathy, the blood p, p’-DDE distributions were similar in different severity of interstitial lesions.

Discussion

Pesticide level in CKD patients and the association with chronic kidney disease was first discussed in Chinese subjects in our study. In the present study, the etiology of patients we enrolled were glomerulonephritis (85.9%) and diabetic nephropathy (14.1%), and we detected 26 types of pesticides or their metabolites. It has revealed that p, p'-DDE is the most common pesticide detectable in our subjects, as p, p’-DDE is the most stable metabolite of DDT in human body. There was significant difference in the positive rate and blood level of p, p'-DDE in the CKD group as compared to healthy controls. Similar results were reported in some earlier studies, but no significant report is available to compare the increased level of pesticides in glomerulonephritis patients as observed by us. In 1988, Rutten et al. first reported higher blood levels of p, p'-DDE and HCH in uremic patients than healthy controls, but the etiology of CKD was not mentioned in the study[Rutten, et al. 1988]. In 2012, Siddharth et al.[Siddharth, et al. 2012] observed increased blood levels of total pesticide and p, p'-DDE in non-diabetic CKD patient in comparison with healthy controls, but no specific etiology were mentioned. In 2017, Ghosh et al.[Ghosh, Siddarth, Singh, Tyagi, Kare, Banerjee, Kalra and Tripathi 2017] reported higher level of some pesticides including p, p’-DDE in CKDu and CKD of known etiology (CKDk) than healthy controls, but the established etiology of CKDk patients were mostly diabetes, and only 14% were glomerulonephritis. Therefore, it appears that CKD patients tend to have higher blood level of pesticides, and the increased level of p, p’-DDE in CKD patients of our study indicating that p, p’-DDE may be involved in the development of CKD due to glomerulonephritis and diabetic nephropathy.

We also found the blood p, p'-DDE concentration in DN subgroup was significantly higher than GN subgroup or healthy controls, suggesting p, p’-DDE seems to have a specific and close relationships with diabetic nephropathy. Although the reason and mechanism were not quite clear, there were several studies presented the association of organochlorine pesticide with diabetics and diabetic nephropathy. There is growing evidence that low-dose exposure to persistent organic pollutants (POPs) is linked to type 2 diabetes[Lee, et al. 2011;Lee, et al. 2006;Lee, et al. 2010;Rylander, et al. 2005], and a study by Brian A. Grice, et al. [Grice, et al. 2017]showed that some POPs such as polychlorinated biphenyls (PCB) increase the risk of ESRD among persons with type 2 diabetes. A study by Everett et al. [Everett, et al. 2017]had reported blood p, p'-DDE as a risk factor for diabetic nephropathy, and an early study from them[Everett and Thompson 2015]showed p, p’-DDT was significantly associated with total diabetes with nephropathy.

Our study revealed that patients with high concentration of p, p’-DDE(≥3.7ng/ml) were older and had lower eGFR and higher 24-hour urinary protein. Correlation analysis showed negative correlation of blood p, p’-DDE with eGFR and positive correlation with 24-hour urinary protein. Also, logistic regression showed p, p’-DDE[OR=3.211]as a risk factor for CKD, adjusting for age and diabetes. As we know, the pesticide DDT and its metabolite p, p'-DDE are

stable, and they degrade slowly in crops and environment, and their fat solubility makes them easy to accumulate in human fat and bio-enriched through the food chain, so older people accumulate more p, p’-DDE.

Although the mechanism of the link between p, p’-DDE accumulation and the decline of renal function is unclear, there were some animal studies demonstrating the glomerular, tubular, and interstitial lesions in OCPs exposed subjects（Choudhary, et al. 2003;Marouani, et al. 2017;Sonne, et al. 2008）. There were also some insights, that is, OCPs may accumulate in the body due to poor excretory capacity of CKD patients with decreasing renal function, and it is possible that accumulated pesticides may induce oxidative stress through mitogen-activated protein kinase (MAPK) pathway in CKD patients which accelerating renal injury progression（Ledirac, et al. 2005;Santos, et al. 2021;Siddharth, Datta, Bansal, Mustafa, Banerjee, Kalra and Tripathi 2012）. In a review on effect of environmental chemicals on renal function, authors proposed that excessive oxidative stress alters the podocyte cytoskeleton leading to albuminuria, podocyte loss, tubular injury and tubulointerstitial fibrosis（Kataria, Trasande and Trachtman 2015）. It was reported that the polymorphism of glutathione-S-transferase (GST) gene was playing a role in increased level of pesticide in CKD, and GSTM1(-)/GSTT1(-) genotype increased the accumulation of pesticides in human body, and was associated with higher oxidative stress in CKD（Datta, et al. 2010;Siddarth, et al. 2014）. Thus, according to the previous research, Pesticide-induced oxidative stress can result from excessive ROS generation. Figure 1 illustrates the possible mechanism of pesticide induced kidney injury. Exposure to pesticides results in the activation of ERK1/2 signaling pathway in addition, these molecules induce the generation of intracellular ROS, which appears to be critical for the pesticide-induced MAPK activation.

Our study showed no correlation between p, p’-DDE levels and the types of glomerulonephritis， but interestingly we found a positive relationship between p, p’-DDE levels and severity of interstitial lesions in MN subgroup, but not in other types of glomerulonephritis. As we know, interstitial lesions were not prominent in MN, so maybe renal interstitial damage linked to pesticide was more likely to be reflected in MN patients.

Conclusion

The current study showed the most common pesticide detectable in Chinese population were p, p'-DDE. It reveals association between increased blood p, p'-DDE concentration and development of CKD with established etiology of glomerulonephritis and diabetic nephropathy.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Ruijin Hospital affiliated to Shanghai Jiaotong university school of medicine.

Consent for publication

Not applicable

Availability of data and materials

The data generated or analyzed during the current study are not publicly available due to obligations of secrecy, but are available from the corresponding author on reasonable request.

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Competing interests

The authors have no relevant financial or non-financial interests to disclose

Author contributions

Weiming Wang: conceptualization and methodology; **Xiaojing Wu**: methodology, data collection, formal analysis, and first draft writing; **Xin Li**: data collection and formal analysis; **Muyin Zhang**: data collection; **Lili Xu**: data collection. **All authors** commented on previous versions of the manuscript. **All authors** read and approved the final manuscript.

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Tables

Table 1. Demographic features and biochemical parameters of the study subjects

Characteristics	CKD patients (n=128)	Healthy controls (n=49)	Statistical value	P value
Age (years)	44.7±15.8	44.4±10.5	T=0.154	0.878
Gender (M/F)	75/33	26/23	c2=0.227	0.634
eGFR (ml/min/1.73m^2)	78.8 (55.4-97.0)	93.4 (88.7~100.5)	Z=-3.692	0.000**
Hemoglobin (g/l)	125.5±22.1	143.9±17.5	T=-5.179	0.000**
Serum uric acid (mmol/l)	410.6±107.0	340.2±80.1	T=4.143	0.000**
Total cholesterol (mmol/l)	6.68±3.16	5.55±1.30	T=3.327	0.001**
Total triglyceride (mmol/l)	2.45±1.66	1.77±1.30	T=2.583	0.011*

eGFR (estimated glomerular filtration rate) was calculated with the chronic kidney disease epidemiology collaboration (CKD-EPI) equation.

*p value is significant at (0.05) **p value is significant at (0.01

Table 2. Clinical features of DN patients and GN patients

Characteristics	DN（n=18）	GN（n=110）	Statistical value	P value
Age（years）	58.5±13.1	42.4±15.1	T=-4.262	0.000**
Gender（M/F）	10/8	63/47	c^2=0.019	0.891
BMI（kg/m^2）	26.9±3.2	24.1±3.4	T=-3.405	0.002**
eGFR（ml/min/1.73m^2）	55.0（35.6-71.2）	86.0（57.3-98.5）	Z=-3.819	0.000**
24h urinary protein(g/24h）	6.01±4.28	4.16±4.05	T=-1.709	0.101
Albumin（g/l）	31.2±7.1	32.3±9.8	T=0.509	0.616
Hemoglobin（g/l）	104.2±23.5	128.7±19.9	T=4.714	0.000**
Hypertension（%）	100%	47.3%	c^2=17.355	0.000**

*p value is significant at （0.05）**p value is significant at （0.01

Table 3 Clinical features in different blood level of p, p'-DDE

Parameters	L1(n=57)	L2(n=28)	L3(n=43)	Statistical value	P value	Pairwise significance
Age（years）	39.4±13.5	42.0±16.9	56.8±11.7	16.926	0.000**	L1vsL2=0.408 L1vsL3=0.000** L2vsL3=0.000**
Gender（M%）	56.3%	61.3%	56.3%	0.244	0.885	
BMI (kg/m^2)	24.6±4.0	23.9±2.6	24.8±3.0	0.607	0.547	
eGFR(ml/min/1.73m^2)	81.1±24.8	86.4±29.6	60.2±26.9	9.1	0.000**	L1vsL2=0.361 L1vsL3=0.000** L2vsL3=0.000**
24h-UP (g/24h)	3.85±3.54	3.95±4.27	5.89±4.06	2.864	0.061	L1vsL2=0.912 L1vsL3=0.024* L2vsL3=0.061
Albumin(g/l)	32.8±9.4	33.2±10.2	29.6±9.1	1.368	0.259	
HB (g/l)	126.9±23.6	129.1±22.0	118.3±17.8	2.210	0.114	
HT（%）	45.3%	54.8%	71.9%	6.071	0.048*	
Diabetes（%）	14.1%	12.9%	28.1%	3.505	0.173	

*p value is significant at 0.05**p value is significant at 0.01

L 1: p, p'-DDE0.85ng/ml, L2: 0.85≤p, p'-DDE3.7ng/ml, L3: p, p'-DDE≥3.7ng/ml

Table 4. Spearman's correlation coefficient between p, p'-DDE, eGFR, and 24h urinary protein

Variables in correlation analysis	Correlation coefficient	P value
p, p'-DDE and eGFR	-0.263	0.003
p, p'-DDE and 24h urinary protein	0.22	0.013

Table 5 Logistic regression analysis for association of p, p'-DDE with CKD

Parameters	B	S.E.	P value	ExpB	ExpB95% CI	
					lower limit	upper limit
Age	-0.042	0.016	0.009	0.959	0.929	0.990
Diabetes	1.070	0.679	0.115	2.915	0.770	11.032
p, p'-DDE	1.166	0.322	0.000	3.211	1.708	6.034

Table 6. blood p, p'-DDE distribution in different severity of interstitial lesions in MN patients

Severity of interstitial lesions	Different levels of blood p, p'-DDE		
	L1 (0.85ng/ml)	L2 (0.85~3.7ng/ml)	L3 (≥3.7ng/ml)
Level 0 (No)	5 (83.3%)	0 (0%)	1 (16.7%)
Level 1 (Light)	5 (21.7%)	9 (39.1%)	9 (39.1%)

Figures

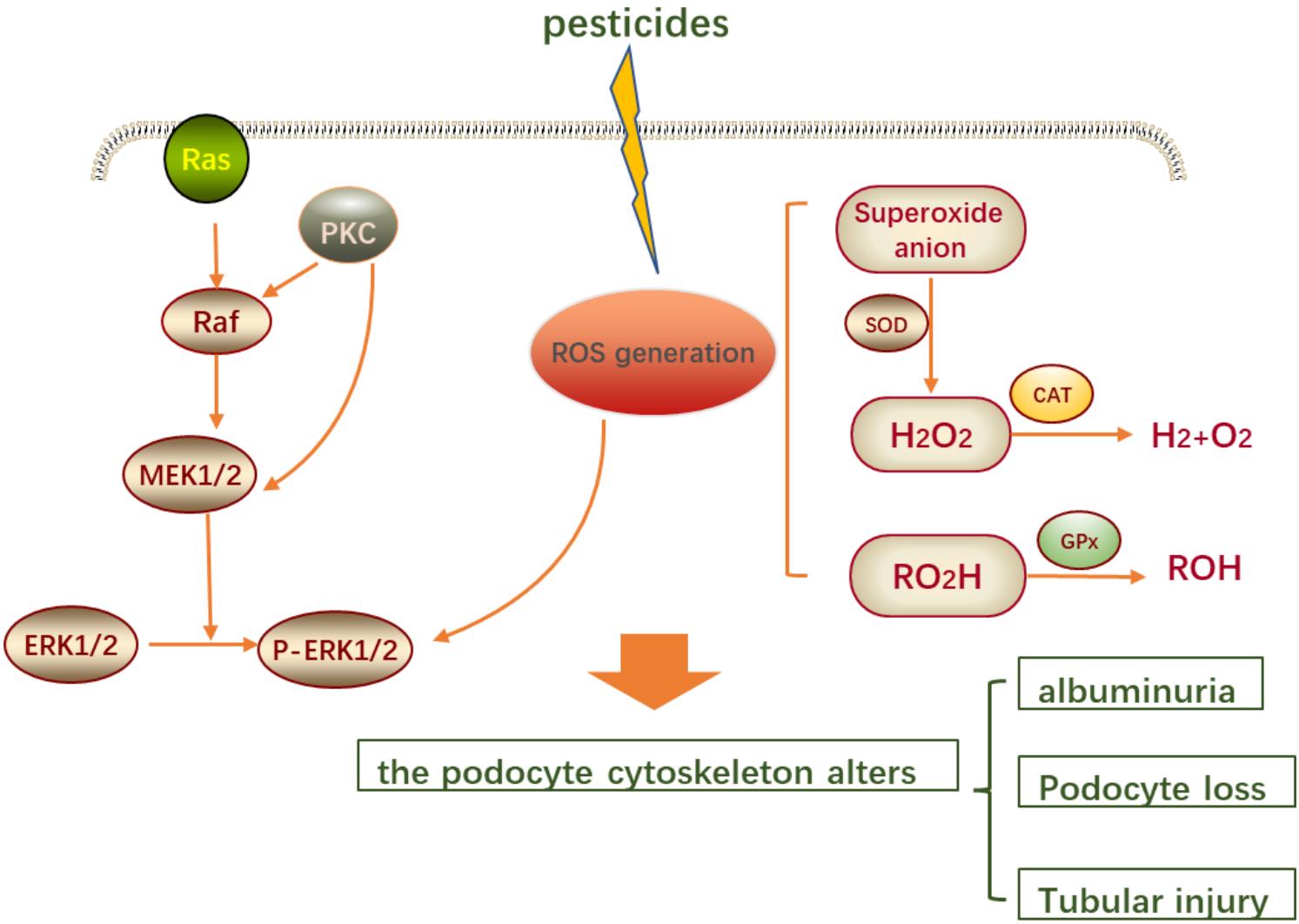

Figure 1

The possible mechanism of pesticide induced kidney injury.

Pesticide-induced oxidative stress can result from excessive ROS generation. Exposure to pesticides results in the activation of ERK1/2 signaling pathway. In addition, these molecules induce the generation of intracellular ROS, which appears to be critical for the pesticide-induced MAPK activation.