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Research Article

Alteration of Metal Element Homeostasis by Cisplatin Treatment

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Abstract

Cisplatin chemotherapy causes several metabolic alterations in the living system. One of these is the modification of element level in the body fluids and organs resulting modified element correlations. Therefore the purpose of this study was to calculate the correlations between element pairs. In a rat experiment, animals were treated with cisplatin by injected i.p. with a single dose of 6.5 mg/kg body weight, while the control group received 1% (w/v) methyl cellulose at 10 mL/kg body weight, p.o. by gastric gavage twice daily for 14 days. Inductively coupled plasma optical emission spectrometry (ICP-OES) was used for measuring Al, As, B, Ba, Ca, Cd, Co, Cr, Cu, K, Li, Mg, Mn, Mo, Na, Ni, P, Pb, Pt, S, Sb, Si, Sn, Sr, V, Zn content, and polarography was used to determine Se content in the plasma and kidney of rats. From the results, correlation calculations were made. The results show that most of the significant correlations in the plasma of control rats remained in the plasma of cisplatin treated rats that prove the fast hydrolysis and excretion of cisplatin from the blood. In the kidney where the platinum accumulation changes the element level at a higher rate, the correlations significantly modified and remained only for 5 element pairs (Mg-P, Mg-S, Mg-Zn, P-S and S-Zn).

ABBREVIATIONS

ICP-OES: Inductively Coupled Plasma-Optical Emission Spectrometry

INTRODUCTION

During formation of cancer, several unwanted metabolic processes occur, and one of these is the alteration of metal element homeostasis that can lead to malnutrition or accumulation of certain elements in different cells. It is proven that the copper level of serum is higher in cancer patients than in healthy people and tumor tissue accumulates copper in a higher rate than other normal tissues. At the same time, the zinc, iron and selenium levels were found to be lower in cancer patients [1]. For avoiding the deficiency state in cancer or during cancer treatment supplementation of different essential components, like vitamins, mineral elements are needed [2]. Several cancer therapies exist depending on for example the type and severity of the cancer. Therapy with metal complexes belongs to the chemotherapy from which one of the most popular is the use of cisplatin for different cancer types [3-5].

Cisplatin has a toxic effect. It is able to bound to different biological molecules like DNA or moderate their structure or synthesis [6,7]. The most known toxic effect is the accumulation of platinum in the kidney causing renal damage [8-12]. This process alters the metal element homeostasis. Since cisplatin rapidly hydrolyses in the plasma by connecting to the plasma proteins then it is transferred to different organs where is accumulated, it is supposed that the higher altered metal element homeostasis is available in organs where platinum accumulates. Therefore statistical analysis was made for determination of the changes of metal element correlation in control and cisplatin treated rats' plasma and kidney.

MATERIALS AND METHODS

Rat experiment

Twenty 8-week-old young male Wistarrats weighting 175-190g were randomly divided into 2 groups (n=10/group). The control group received 1% (w/v) methyl cellulose at 10mL/kg body weight p.o. by gastric gavage twice daily for 14 days. The cisplatin treated group received cisplatin (TEVA, Israel) by intraperitoneal injection with a single dose of 6.5mg/kg body weight in 10mL/kg 1% methyl cellulose mucin vehicle [13-15]. For proving the effect of cisplatin to renal dysfunction, blood urea nitrogen (BUN) and creatinine levels were measured on day 12 besides general routine parameters [14,15]. On the 14th

day the rats were weighted then terminally anaesthetized with pentobarbitone.

The animals were kept individually under standard conventional conditions according to European Council Directive 123. The study conformed to the Declaration of Helsinki guidelines and was approved by the local animal ethical committee.

Animal samples

The blood was collected on the 14th day by thoracic vena puncture and was anticoagulated with citrate and centrifuged twice at 2500rpm for 10 min at +4°C to obtain plasma. The kidneys were removed, washed and weighed.

Measurement of metal content

Plasma and kidney samples were measured (1g plasma, 1g kidney) into the digestion vessels. For digestion, 5mL 65% nitric acid and 2mL hydrogen peroxide were used in the case of plasma, while 10mL 65% nitric acid and 2mL hydrogen peroxide were applied for the kidney samples. The digestion was made in block digestion system. After digestion and evaporation, the samples were poured over into 10mL flask and were filled up with bidistilled water to mark.

Inductively coupled plasma optical emission spectrometric (ICP-OES) method was used for measuring Al, As, B, Ba, Ca, Cd, Co, Cr, Cu, K, Li, Mg, Mn, Mo, Na, Ni, P, Pb, Pt, S, Sb, Si, Sn, Sr, V, Zn content [11] with a Spectro Genesis ICP-OES (Kleve, Germany)equipment by the method applied earlier [16]. For the standardization of equipment and measurements, Spectro multi-element and Spectrum 3D standards were used. Standards were prepared in the same matrix as the samples.

Computer guided TraceLab 50 type polarographic analyzer was used for the determination of selenium content by square wave voltammetric measurement on hanging mercury (working) electrode and in the presence of reference electrode (silver/silver chloride) and counter electrode (platinum) at -550 mV [17].

General routine parameters, redox parameters, element concentration in plasma, histological investigations and element content changes in kidney were published earlier [14,15]. Earlier the average element content of plasma and kidney in control group was compared to that of in cisplatin treated group independently from the individual animals, since only the means were calculated from the individual results and the average values were compared.

Statistical calculations

The correlations between elements were calculated from the results with Statistica 13.1., Dell Inc. (2016). Dell Statistica (data analysis software system), version 13. software.dell.com. Significance was set at $P<0.05$.

RESULTS AND DISCUSSION

The fast degradation and transfer of cisplatin into the organs is proven by the similar correlation for numerous element pairs in plasma of control and cisplatin treated group (Table 1). In the case of Mn-S and S-Zn pairs, the correlations became reverse by the effect of cisplatin treatment. At the same time several correlations, which are found to be significant in the control group (Table 2), disappear in the cisplatin treated group appearing other new correlations by the effect of cisplatin treatment (Table 3). It is known the essential element absorption, transfer and excretion are rigorously controlled and the administration of certain essential or toxic element in high amount changes the whole metal element homeostasis [18]. This process is not always discoverable for the first moment and in plasma in the case of a single dose as for cisplatin mainly if the agent disappears relatively fast from the blood. After the absorption of cisplatin fifty percent of it transforms to different metabolites, bounds rapidly to high molecular weight proteins and low molecular weight other compounds and cisplatin aqua complexes also form within one hour [19]. Later but within one day the total amount of cisplatin transforms to some metabolites [*20*]. But this short time effect also modifies some element levels and correlations significantly as it can be seen according to the statistical calculations and our earlier papers [14,15].

The correlations are similar for several element pairs in the kidney of the control group (Table 4) as was found in the plasma of control group (Table 1,2), for example in the case of Ba-Ca, Ca-Mn, Fe-K, Fe-Na, Fe-Si, Fe-Zn, Mg-P, Mn-Sr, Mo-Na, Mo-P, Mo-S, Mo-Si, S-Zn.

There are a lot of correlations in the kidney of the control

Table 1: Corresponding and reverse correlations for elements in the plasma of control and cisplatin treated groups ($P<0.05$).

Element pairs	Control group	Cisplatin treated group
Corresponding correlations		
Ba-Cr	0.889	0.943
Ba-Fe	0.906	0.964
Ba-K	-0.816	-0.784
Ba-Mn	0.860	0.851
Ba-Na	0.930	0.966
Ba-Si	0.705	0.961
Ba-Zn	0.754	0.966
Cr-Fe	0.788	0.971
Cr-Mn	0.679	0.971
Cr-Na	0.784	0.965
Fe-K	-0.702	-0.767
Fe-Mn	0.751	0.869
Fe-Mo	0.803	0.978
Fe-Si	0.830	0.978
Fe-Zn	0.771	0.991
K-Na	-0.795	-0.805
K-Sr	-0.888	0.770
Mn-Na	0.708	0.823
Mn-Zn	0.0869	0.901
Ni-Zn	0.904	0.830
Reverse correlations		
Mn-S	0.682	-0.881
S-Zn	0.723	-0.831

Table 2: Element correlations in the plasma of control group.

Element pairs	Correlation	Element pairs	Correlation
Al-Ca	0.797	Ca-K	-0.740
Al-Mn	0.760	Ca-Mn	0.868
Al-S	0.680	Mg-P	0.707
Al-Zn	0.776	Mn-Sr	0.800
Ba-Ca	0.730	Mo-Si	0.936
Ba-Sr	0.786	Na-Si	0.745
Ca-Fe	0.711	Ni-S	0.733

Table 3: Element correlations in the plasma of cisplatin treated group.

Element pairs	Correlation	Element pairs	Correlation
Ba-Cu	0,863	Fe-Ni	0,802
Ba-Mo	0,914	Fe-P	-0,828
Ba-Ni	0,841	Fe-S	-0,846
Ba-P	-0,859	K-Mo	-0,763
Ba-S	-0,863	K-P	0,755
Ca-Sr	0,937	K-Si	-0,842
Cr-Cu	0,880	K-Zn	-0,716
Cr-Mo	0,970	Mn-Mo	0,768
Cr-Ni	0,776	Mn-P	-0,720
Cr-P	-0,865	Mn-Si	0,840
Cr-S	-0,819	Mo-Na	0,979
Cr-Si	0,952	Mo-Ni	0,773
Cr-Zn	0,959	Mo-P	-0,810
Cu-Fe	0,897	Mo-S	-0,768
Cu-K	-0,800	Mo-Si	0,956
Cu-Mo	0,934	Mo-Zn	0,952
Ca-Na	0,902	Ni-Si	0,776
Cu-Ni	0,724	P-S	0,832
Cu-P	-0,768	P-Si	-0,889
Cu-Si	0,863	P-Zn	-0,791
Cu-Zn	0,871	S-Si	-0,907
		Si-Zn	0,956

Table 4: Correlations for elements in the kidney of control and some corresponding correlation in the kidney of cisplatin treated group (P<0.05).

Element pairs	Control	Cisplatin treated
Ba-Ca	0.889	
Ba-Co	0.786	
Ba-P	-0.687	
Ba-Sr	0.906	
Ca-Co	0.770	
Ca-Mn	0.895	
Ca-Sr	0.958	
Co-Sr	0.733	
Fe-K	-0.756	
Fe-Mg	0.832	
Fe-Na	-0.689	
Fe-P	0.779	
Fe-S	0.836	
FeSi	-0.841	
Fe-Zn	0.817	
Mg-Mo	-0.778	
Mg-Na	-0.79	
Mg-P	0.967	0.939
Mg-S	0.978	0.893
Mg-Si	-0.848	
Mg-Zn	0.747	0.913
Mn-Sr	0.864	
Mo-Na	0.929	
Mo-P	-0.826	
Mo-S	-0.792	
Mo-Si	0.706	
Na-P	-0.845	
Na-S	-0.815	
Na-Si	0.784	
P-S	0.963	0.989
P-Si	-0.779	
S-Si	-0.785	
S-Zn	0.754	0.978
Si	-0.884	

Table 5: Correlations for element pairs characteristic only in the kidney of cisplatin treated group (P<0.05).

Element pairs	Correlation
Ba-Fe	0.941
Ca-Mg	0.798
Cu-Fe	0.756
Cu-Mn	0.746
Cu-S	0.808
Cu-Zn	0.772
Mn-S	0.754
Mn-Zn	0.725
Na-Sr	0.753
P-Zn	0.980
Pt-Mo	-0.893
Se-Sn	0.714

group from which only some remained in the cisplatin treated group as it can be seen in Table 4 for Mg-P, Mg-S, Mg-Zn P-S and S-Zn. Nevertheless, by the effect of cisplatin treatment, some new correlations figure in the cisplatin treated group (Table 5). These more significant changes in the element correlations of kidney also show the more harmful effect of cisplatin on the kidney. This strengthens our earlier findings and some authors' statements that depletion of essential element and accumulation of toxic heavy metals occur by the cisplatin treatment [13,14,21,22].

The correlation changes were bigger in the kidney than it was in the plasma. This is understandable since cisplatin disappears from the blood during some hours while it accumulates in the kidney where its effect is more drastic to the element concentrations and causing element deficiency as well [8-12,23].

Plasma showed more significant element content differences between control and cisplatin treated groups [14,15], nevertheless according to the present statistical calculations the correlation between element level with other element level for the individual rats and their direction of correlations are similar

in both groups. These show that cisplatin notably affects on the element concentration of plasma but the metabolic processes and element relationships in plasma do not alter basically. In the case of kidney there are only a few significant element content differences between control and cisplatin treated groups [14,15] causing by the higher element content differences with higher standard deviation between the individual animals, but the correlations for the elements between the control and cisplatin treated groups totally changed. This also confirms our earlier statement that cisplatin causes the highest alteration and injury in the organ where it is accumulated [15].

The cisplatin treatment is a drastic therapy to the patients and several metabolic changes could be observable. According to these results and further experiments we could understand the action of cisplatin in details and the metabolic changes by which we can give recommendation to the doctors and patients for nutrition and supplementation.

CONCLUSION

The changes of element metabolism by the treatment of cisplatin was noticeable at a higher rate in the kidney than in the plasma since several relevant correlations were left in the plasma while most of the correlations changed in the kidney. Besides the element content, the correlations should also have to calculate to monitor the element homeostasis alteration since according to the calculation the homeostasis changes can be observable more detailed.

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