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Interference of Cd^{++} on the Turnover of Zinc Orally Administered

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Results of zinc distribution rates orally administrated to guinea pig and influence on its turnover by Cd^{++} are given. No biological function for cadmium has been found yet, althought the metalotioneine from kidney with fixed contents of zinc and cadmium has been isolated. The higher affinity of this cation for the thiol groups of a number of enzymes containing zinc appears to be responsible for its toxicity even in very small quantities.

Exponential functions representig variations of zinc distribution has been determined.

Cadmium ions disturb the zinc metabolism causing a delay in its assimilation. A competition between Zn^{++} and Cd^{++} can be admitted, taking corresponding to the 60th day.

The importance of trace elements in biochemistry well recognised (5, 6). The role that zinc plays as a component of numerous metalenzymes has been reviewed by different authors (4, 20). The dysfunctions produced by the lack of this element are analogous to those encountered, when sufficiente zinc exists but the amounts of cadmium are elevated (7). Cadmium is an element to which no definite function has been attributed up to now. However, since it is inevitably allied to zinc, as much in the geosphere as in the biosphere (19) it is possible that it interferes with zinc metabolism (20). The kidneys of a new-born contain cadmium, in very low proportions (18), but in adults the levels of cadmium rise and seem to be correlated with the disorders caused by arterial hypertension (17). SCHREODER (16) has proven this experimentally in rats.

The series of studies carried out by CARROLL in 28 cities of the United States have corroborated this hypertensive action of cadmium (2).

VALLÉE and his coworkers have isolated a metalprotein: thioneine (14) which contains cadmium in fixed quantities, greater than those of zinc; although its action is not known, it is possible to attribute a biological role to cadmium, and not merely the toxic role which has been attributed to it until now (10).

The data in the literature are not concordant (1, 8), and as a continuation of our work on the turnover of zinc in mammals (11, 12), we have studied the interference produced by low levels of cad-

mium on the metabolism of orally administered zinc in guinea pigs. In this paper the retention curves of zinc in the most important organs and tissues is described in mathematical form and the influence of cadmium on these curves is discussed.

Results

Osseous-muscular system (carcass). The equation which governs the process is:

$$y = 5.83e^{-0.023t}$$

«y» represents the percentage of the quantity of zinc in day «t».

We show (figure 1, broken line) a slow and continuous diminution that goes from 5 to 0.75 % during the period of study, which was from 5 to 120 days. The calculation gives a mean biological half life of 30 day.

In the continuous line, we show the variations of the content of Zn-65 in the presence of Cd. It attains a maximum after 30 days with a value of 10 % of the administered amount of zinc and after 60 days reaches a minimum of 0.06 %, to arrive at 3 % after 90 days.

Skin + hair system. The broken line (figure 2) for this system shows a diminution from 2 to 1 % from 5-15 days. After this date, the quantity of Zn-65 stays practically constant, which shows us, therefore, that the skin + hair acts as a retentive medium for zinc, in accordance with the value of the coefficient of the equation:

$$y = 1.18e^{0.0005t}$$

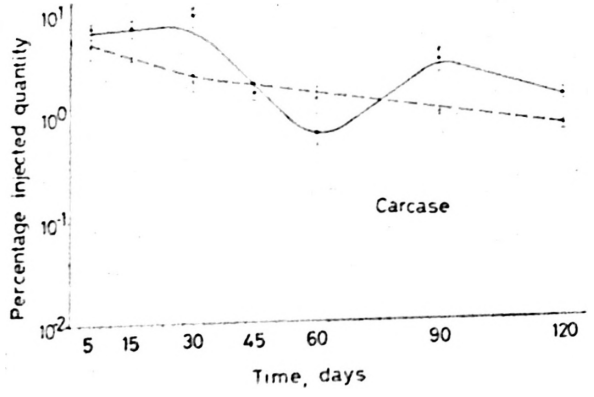

Fig. 1. *Changes of zinc content in carcasse related to time of administration.*

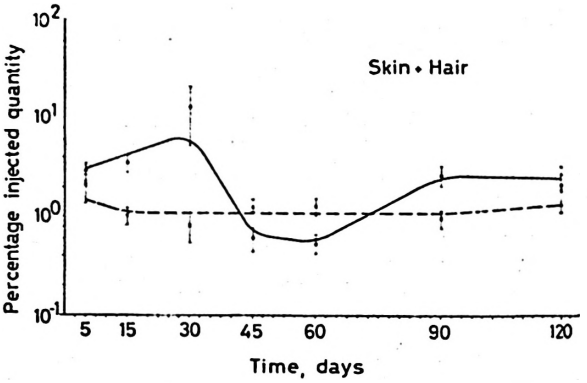

Fig. 2. *Changes of zinc content in skin plus hair in relation to time of administration.*

When Zn-65 is adiminstered with Cd the distribution is markedly affected (continuous line); we see a maximum after 30 days and a minimum after 60, passing from 13 to 0.5 %.

Examination of the broken curves of figure 1 and 2, suggests that the osseous-muscular and skin + hair systems, are accumulatives with time.

Lung. The pattern of retention in this organ corresponds to the formula:

$$y = 0.264e^{-0.1447t} + 0.014e^{-0.0063t}$$

from which we calculated two mean biological half lives of 5 and 110 days.

In the broken line of figure 3, these two periods are clearly marked: the first, which is very rapid, ends after 15 days and the second, which is very slow, lasts until the experiment is finished.

In the continuous line, we see the variation of the concentration when zinc is

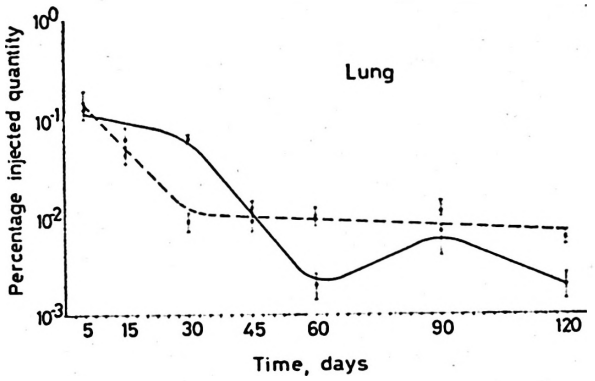

Fig. 3. *Variation of zinc content in lung related to time of administration.*

accompanied by the Cd ion. A slow disminution is observed up to 30 days, which later becomes more rapid, attaining a minimum after 60 days.

Abdominal visceras. The abdominal viscera exhibit rapid assimilation and disassimilation and the metabolic process is analogous in all of the. The liver corresponds to the equation:

$$y = 2.53e^{-0.2102t} + 0.01e^{-0.0041t}$$

In figure 4, we can see in the broken line a very rapid diminution from 5 to 30 days, with a mean biological half life of approximately 3 days. A second period follows from 30 to 120 days in which the loss occurs more slowly with a mean biological half life of 169 days.

The continuous line corresponds to the zinc + cadmium process and a pronounced perturbation, analogous to the cases studied previously, is observed, falling from 0.78 % to a 0.026 % with a minimum at 60 days.

Reproductive organs: Genital apparatus. The complete exponential function which corresponds to this organ is:

$$y = 0.166e^{-0.0754t} + 0.035e^{-0.0070t}$$

In figure 5, broken line, the phase of accumulation has already terminated on the 5th day of administration, as in those mentioned previously. After this day, two periods are marked: in the first it is rapid up to approximately the 30th day, with a mean biological half life of 9 days. Another period follows which embraces the period up to 120 days in which the retention shows a mean biological half life of 99 days.

The distribution of zinc was affected in the same way as in the other organs due to the presence of the cadmium ion (continuous line) but from the 5th to the 30th day, the amount of zinc remained practically constant. It decreases to a minimum

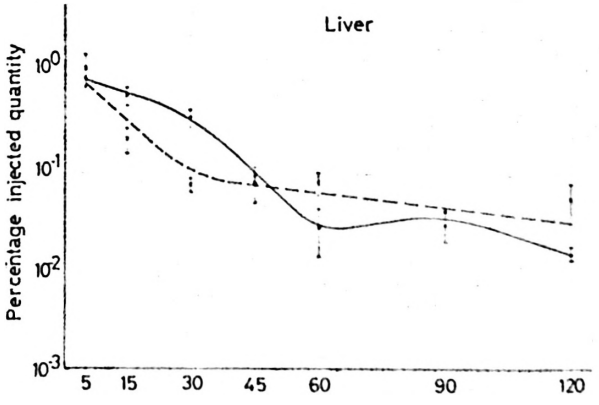

Fig. 4. *Changes of zinc content in liver in relation to time of administration.*

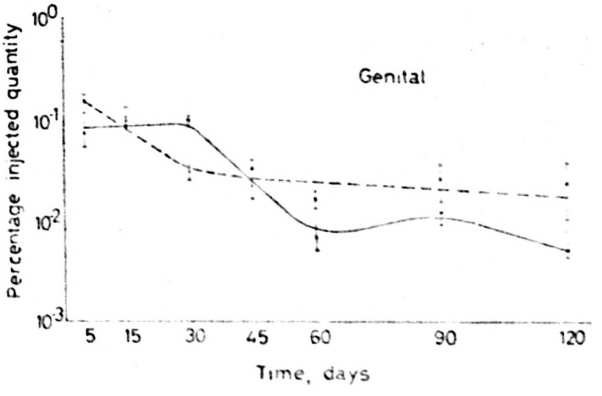

Fig. 5. *Variation of zinc content in genitals related to time of administration.*

Table I. *Zn-65, quantity averages in the different part of body in function of the time since oral injection of Zn-65.*

Part of body	PORCENTAGE OF THE QUANTITY ADMINISTRED						
	5 days after	15 days	30 days	45 days	60 days	90 days	120 days
Total body	10.398 ± 2.094	5.60 ± 0.883	6.90 ± 3.405	4.02 ± 0.526	3.180 ± 0.705	2.29 ± 0.52	3.28 ± 0.774
Carcass	5.075 ± 1.185	3.70 ± 0.777	2.226 ± 0.418	2.07 ± 0.002	1.460 ± 0.002	1.014 ± 0.030	0.761 ± 0.088
Skin + Hair	2.049 ± 0.664	1.04 ± 0.157	0.821 ± 0.279	1.385 ± 0.200	1.282 ± 0.263	0.982 ± 0.214	1,93 ± 0.834
Central Nervous System	0.051 ± 0.011	0.024 ± 0.003	0.011 ± 0.002	0.017 ± 0.003	0.012 ± 0.003	0.005 ± 0.002	0.004 ± 0.0002
Pancreas	0.071 ± 0.023	0.019 ± 0.003	0.007 ± 0.002	0.011 ± 0.004	0.007 ± 0.002	0.032 ± 0.030	0.002 ± 0.0008
Liver	0.971 ± 0.329	0.192 ± 0.054	0.068 ± 0.009	0.081 ± 0.007	0.072 ± 0.015	0.027 ± 0.009	0.405 ± 0.357
Spleen	0.037 ± 0.008	0.007 ± 0.001	0.004 ± 0.0009	0.003 ± 0.0006	0.006 ± 0.001	0.003 ± 0.002	0.004 ± 0.002
Stomach	0.141 ± 0.054	0.026 ± 0.006	0.009 ± 0.002	0.012 ± 0.003	0.008 ± 0.001	0.008 ± 0.002	0.003 ± 0.0007
Intestine	0.889 ± 0.325	0.172 ± 0.057	0.051 ± 0.005	0.081 ± 0.020	0.077 ± 0.022	0.041 ± 0.018	0.020 ± 0.003
Kidney	0.248 ± 0.108	0.069 ± 0.011	0.014 ± 0.003	0.024 ± 0.005	0.019 ± 0.005	0.015 ± 0.008	0.012 ± 0.003
Genitals	0.148 ± 0.031	0.085 ± 0.011	0.030 ± 0.005	0.032 ± 0.007	0.016 ± 0.003	0.025 ± 0.010	0.023 ± 0.013
Lung	0.142 ± 0.044	0.043 ± 0.008	0.009 ± 0.002	0.012 ± 0.002	0.010 ± 0.002	0.011 ± 0.003	0.006 ± 0.001
Heart	0.069 ± 0.019	0.019 ± 0.004	0.004 ± 0.001	0.006 ± 0.0006	0.006 ± 0.002	0.004 ± 0.002	0.006 ± 0.003

Table II. *Zn-65, quantity averages in the different part of body in function of the time since oral injection of Zn-65 + Cd.*

Part of body	PORCENTAGE OF THE QUANTITY ADMINISTRED						
	5 days after	15 days	30 days	45 days	60 days	90 days	120 days
Total body	13.91 ± 2.116	13.25 ± 2.700	27.36 ± 8.68	2.78 ± 0.519	1.409 ± 0.002	6.37 ± 0.003	4.04 ± 1.135
Carcass	7.86 ± 0.894	7.79 ± 1.631	10.03 ± 2.04	1.79 ± 0.382	0.662 ± 0.115	3.43 ± 0.830	1.56 ± 0.200
Skin + Hair	2.89 ± 0.600	3.546 ± 0.731	13.30 ± 8.12	0.618 ± 0.178	0.544 ± 0.116	2.66 ± 0.590	2.17 ± 1.048
Central Nervous System	0.034 ± 0.007	0.053 ± 0.011	0.093 ± 0.009	0.014 ± 0.003	0.008 ± 0.0006	0.017 ± 0.002	0.008 ± 0.003
Pancreas	0.045 ± 0.014	0.031 ± 0.008	0.031 ± 0.004	0.005 ± 0.001	0.002 ± 0.0006	0.003 ± 0.0004	0.001 ± 0.0005
Liver	0.784 ± 0.163	0.508 ± 0.098	0.311 ± 0.063	0.072 ± 0.028	0.026 ± 0.013	0.036 ± 0.003	0.014 ± 0.002
Spleen	0.032 ± 0.006	0.011 ± 0.002	0.009 ± 0.002	0.003 ± 0.0006	0.001 ± 0.0004	0.002 ± 0.0004	0.0008 ± 0.0003
Stomach	0.131 ± 0.047	0.050 ± 0.010	0.032 ± 0.004	0.009 ± 0.003	0.003 ± 0.0007	0.004 ± 0.0004	0.002 ± 0.001
Intestine	1,110 ± 0,036	0.321 ± 0.068	0.268 ± 0.228	0.033 ± 0.009	0.017 ± 0.003	0.023 ± 0.010	0.022 ± 0.014
Kidney	0.237 ± 0.042	0.103 ± 0.027	0.109 ± 0.011	0.009 ± 0.003	0.007 ± 0.002	0.015 ± 0.001	0.004 ± 0.001
Genitals	0.072 ± 0.020	0.107 ± 0.024	0.097 ± 0.008	0.022 ± 0.006	0.007 ± 0.002	0.012 ± 0.003	0.005 ± 0.0007
Lung	0.122 ± 0.022	0.061 ± 0.020	0.061 ± 0.006	0.009 ± 0.002	0.002 ± 0.0006	0.007 ± 0.003	0.002 ± 0.0006
Heart	0.073 ± 0.015	0.032 ± 0.006	0.041 ± 0.005	0.005 ± 0.0008	0.001 ± 0.0009	0.004 ± 0.0005	0.001 ± 0.0001

after 60 days with a significatively low value without further rise up to the conclusion of the experiment. This result is in accordance with other authors (18) who study the influence of cadmium in the metabolism of zinc in masculine genital organs, considered by them as organs typical of retaining zinc.

Discussion

From the data given here and from our other studies on the metabolism of orally administered zinc in the guiena pig we may deduce:

That in the organs and viscera, both thoracic and abdominal, the period which we may designate as accumulative, has a duration of less than 5 days, but after this time, all the representative curves show elimination, pointing out two well defined periods with mean biological half life in the order of 10^1 and 10^2 days, calculated from the two terms of the corresponding equation.

In the skin + hair and carcass systems, the curves are continuous and correspond to an equation of only one term per quantum, and a mean biological half life may be calculated which in the case of the skin + hair system, is practivally infinite, due to its being a 100 % accumulative organ.

When cadmium is incorporated into the Zn-65 solution, there are evident variations in accordance with other author (13) and with our previous works (15).

The presence of two maxima in the figures of Zn-65 in the 30 and 90 days which we have shown, shows, a delay in the incorporation of zinc and that the assimilation occurs in more than one period.

Due to the competitive action between the zinc and cadmium ions, pointed out by various authors (3), regarding the reaction with the thiol groups of cysteine and glutation with a preponderance of the cadmium protein union with respect to the zinc protein, we suggest that action, takes place between 30 and 90 days, the maximum value correlating with a minimum of zinc, since curves show a minimum on the 60th day.

Resumen

Se estudia la distribución del cinc administrado oralmente a cobayas, y la influencia en sus recambios metabólicos por la acción del cadmio. Para el cadmio no ha sido encontrada todavía una función biológica definida, aunque se ha aislado la metaltioneína del riñón que fija dicho metal y también el cinc. La gran afinidad del cadmio para los grupos tiólicos de un cierto número de enzimas que contienen cinc, parece ser la causa fundamental de su toxicidad, aun en muy pequeñas cantidades.

Se han determinado las funciones exponenciales que representan las variaciones de la distribución del cinc en los diferentes tejidos analizados.

Los iones cadmio interfieren el metabolismo del cinc originando un retraso en su asimilación. Puede administrarse una competición entre iones cadmio e iones cinc que, según las pruebas verificadas, tiene lugar entre los 30 y los 90 días, con un máximo que corresponde a los 60 días.

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