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慢性鎘中毒之研究：一般性之影響

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摘 要

以含100ppm鎘(Cadmium)之飲水長期投與之大白鼠，其臟器深受鎘之影響，尤其是肺、心、腦及胸腺等明顯的萎縮($P<0.05$-$P<0.001$)。產生貧血，白血球略高，其中性球百分比反而較少。以血清血尿素氮及肌氨酸的量及血清GOT，GPT及ALP活性加以觀察則鎘對腎及肝功能之影響並不明顯。鎘投與組大白鼠之血液及其他臟器之鋅及鎘累積量則較對照組明顯的增加($P<0.05$-$P<0.001$)。

由以上之結果加以分析，鎘對大白鼠之慢性中毒以肺之萎縮最爲明顯，鎘中毒時腎及肝功能測定並不適宜做爲中毒指標。但血液及其他器官之高鋅及鎘則可供爲參考。

鎘之工業應用導致鎘之嚴重污染[1]，鎘中毒最先發現於日本之痛痛病(ITai-itai disease)[2]。鎘之污染於食物及飲用水常會引起各種不同之病變如高血壓，腎功能不良，動脈硬化及癌等[3-8]。Joshi氏等[9]亦指出鎘之腹腔注射會引起肺水腫，間質性肺炎及腎血管球膜炎等。

鎘之急性中毒，尤其對腎、肝及生殖機能之影響已有很多之鑑定指標物及方法[10-14]。但當動物長期遭受鎘慢性中毒時，則其毒性可能呈現不一致的現象，因鎘在體內之代謝或累積易受食物或環境中其他重金屬如鋅、銅、鐵及鎘等強力的影響[15-18]。故鎘污染地區對慢性中毒之鑑定以何者是最佳測定方法及標的物，仍未十分明瞭。

故本文擬以鎘慢性長期投與大白鼠之臟器重量變化，血液學，血清酵素活性及鋅、鎘含量之差異性等提出報告。

材料及方法

動物飼養及管理：Wistar株大白鼠係購自台大動物中心(體重60-70克)，置於溫度調節之動物室，以任意採食方式飼以普通飼料(台糖公司製品)，俟大白鼠體重達90-95克時實驗組(15隻)開始經飲水自由給予100 ppm之鎘(Cadmium acetate, Wako Chemicals)，對照組(5隻)則給以去離子水連續90天；進行各項試驗之前斷食24小時。小白鼠先以乙醚(Wako Chemicals)麻醉之，稱重後由股動脈採血供各種生化學，血液學檢查及重金屬含量之測定。各種臟器分別取出稱重及測定重金屬累積量。

血球檢查：以hemocytometer測定WBC及RBC數值並做白血球分類，以毛細管計數血容比。

血清生化學檢查：腎功能檢查包括血尿素

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氮(BUN)[19]及肌氨酸(creatinine)[20]。肝功能包括 Alkaline phosphatase(ALP), glutamic oxaloacetic transaminase(GOT)及glutamic pyruric transaminase (GPT)[21]。

重金屬之檢查：以 Dry ashing 方法進行之，灰化物以 Nitric acid 消化之，經去離子水適當稀釋後以 AAS 測定之，其中鋅以 air-acetylene flame，鎘以 graphite-furnace 分別測定之。

數值分析：全部實驗數值以 mean±SD 表示之。實驗組及對照組結果之分析比較及統計學意義之評估以student t test爲之。P 值以≦0.05 表示具統計學上之差異意義。

結　果

使用於大白鼠飼養之飼料其重金屬含量之分析結果如表 1 所示。

鎘對大白鼠內臟重量之影響(表 2)：鎘投與組大白鼠之內臟重量較對照組具非常明顯萎縮，尤其是肺、心、腦及胸腺($P<0.05$-$P<0.001$)。

鎘對血液學之影響(表 3)：鎘投與組之紅血球數($P<0.001$)，血容比等較對照組明顯的減少，白血球則略爲提高，但其中嗜中性球百分比則較對照組少。

Table 1. Heavy Metal Contents of Diet

Heavy metal	Concentration (mg/kg)
Zn	40.15-50.48
Cu	65.41-41.79
Cr	1.82-1.62
Cd	0.18-0.67
Pb	1.74-1.07

Heavy metal levels of all diets were verified by atomic absoption spectrophotometry.

Table 2. Effect of Cadmium Acetate on the Average Weight of the Internal Organs of Rats

Organs @	Administered with (Mean±SD)	
	Cadmium acetate (100 ppm; n=15)	Deionized H_2O (n=5)
Lung	0.50±0.09***#	1.00±0.18
Liver	3.04±0.53	3.50±0.42
Heart	0.30±0.02***	0.40±0.08
Kidney	0.34±0.03	0.37±0.03
Brain	0.60±0.07***	0.78±0.02
Thymus	0.14±0.04*	0.20±0.05
Spleen	0.45±0.22	0.61±0.30
Testis	.....	.....
Body Weight	285.0±39.6**	278.0±25.0

@The organ weight is corrected for body weight (organ weight/body weight) ×100%. Each datum is the mean value expressed on a wet basis.
By Student t test (df=18): *P<0.05,**P<0.01 and ***P<0.001.

鎘對血清酵素之影響(表 4)：鎘中毒大白

Table 3. Hematological Changes Caused by Cadmium acetate Administration in Rats

Subject	Administered with (Mean±DS)	
	Cadmium acetate (100 ppm;n=15)	Deionized H_2O (n=5)
RBC ($\times 10^{-4}$cells/mm^3)	415.8±18.7*	510.0±24.0
WBC (mm^3)	9,453±3,404	8,750±894
Hematocrit (%)	37.7±4.0	38.2±2.4
Differential count (%)		
Neutrophil	25.3±3.3	28.2±2.3
Lymphocytes	74.7±3.3	71.8±2.3

#By Student t test (df=18): *P<0.001.

鼠之腎功能指標如血尿素氮及尿氨酸不具統計學有意義的差異性。對肝功能指標之 ALP，GOT 及 GPT 等亦無統計學上的意義。

鎘投與組大白鼠內臟對鋅及鎘含量如表 5 所示。不但鎘之含量在實驗組之各臟器有明顯的增加($P<0.01$-$P<0.001$)，而且鋅之含量($P<0.05$-$P<0.001$)亦較對照明顯的增加。

討　論

鎘無論經由口服，注射或呼吸進入宿主體後會廣泛地影響所有系統器官[22]。重金屬如鎘、銅及汞對宿主體內之細胞分子如氨基酸，胜肽及蛋白質之-SH 群功能基具非常強烈之親和性引起其毒性作用[23]。Stowe 氏[23]於 1972 年報告，以 160 ppm 鎘($CdCl_2$)連續投與 200 天後，實驗家兎發現生長遲緩、貧血、嗜中性白血球增多，淋巴球減少，血蛋白素減少，巨脾及腎的腫大等。但由本實驗之結果發現，全部實驗動物之內臟器官較對照組都有明顯的萎縮，尤其是肺、心、胸腺及腦($P<0.05$-$P<0.001$)。此種結果差異可能受動物之種類及飼料中其他重金屬含量之影響。

鎘對肺之毒性已被報告過，由我們的結果亦發現肺有明顯的萎縮。此種現象亦發現於重金屬缺乏飼料飼養之大白鼠(未發表之結果)，證明鎘不但具對肺之毒性且不易遭受其他重金屬存在的影響。Cross 氏等[24]以 intratracheal instillation 方法投與鎘 24 小時後，鎘會引起實驗動物肺之 cytosolic lysosmal enzymes 的變化，如 superoxide dismutase,

Table 4. Changes of Creatinine, BUN and Serum Enzymes after Cadmium acetate Administration in Rats

Subject	Administered with (Mean±SD)	
	Cadmium acetate (100 ppm; n=15)	Deionized H_2O (n=5)
Creatinine (mg/dl)	0.71±0.07	0.76±0.06
BUN (mg/dl)	20.7±1.5	21.1±1.0
SALP (u/ml)	3.85±2.42	3.40±1.25
SGOT (u/ml)	166.0±28.4	168.2±32.0
SGPT (u/ml)	37.3±13.3	27.9±12.5

Table 5. Zinc and Cadmium Concentrations (ppm) in the Wet Internal Organs of Cadmium acetate-Administered Rats

Organ	Heavy metal	Cadmium acetate administered (100 ppm; n=15)	Deionized H_2O (Control; n=5)
Blood	Zn	75.5±3.8***	8.0±2.0
	Cd	4.26±0.47**	0.04±0.03
Liver	Zn	82.6±4.7***	31.2±4.5
	Cd	21.51±2.07***	2.32±0.37
Lung	Zn	45.5±2.7**	32.1±15.2
	Cd	2.25±0.25***	0.28±0.14
Spleen	Zn	86.1±24.1*	53.5±23.4
	Cd	7.10±3.44***	0.49±0.16
Kidney	Zn	77.5±23.7**	39.3±13.9
	Cd	25.08±2.37***	4.13±1.18
Brain	Zn	128.0±43.2***	40.6±17.1
	Cd	1.52±0.15***	0.13±0.11
Testes	Zn	35.8±7.8**	22.3±6.2
	Cd	0.75±0.06***	0.16±0.05

#By Student t test (df=18): *P<0.05 **P<0.01 and ***P<0.001.

catalase, 及 glutathion peroxidase-associated enzymes 等明顯的增加，同時亦發現非蛋白 SH (NPSH), TBA-reactive substances，蛋白質及 DNA 的增加。故鎘對肺之毒性，是鎘慢性中毒中最明顯且穩定的變化。

鎘進入宿主後主要累積於肝及腎。由實驗結果發現，所有臟器之鋅濃度較對照組明顯的提高，尤其是腦。鋅之增加會誘導產生 Cd-binding protein[25-26]，此種 metalothionein 在重金屬中毒之調節上扮演很重要的角色[27]。以血清血尿素氮及肌氨酸量實驗組及對照組間無明顯的差異，此種現象亦發現於血清 GOT, GPT 及 ALP 之活性上。故在鎘慢中毒地區，對鎘中毒嚴重程度之評估，若仍依急性毒性行之，則其結果評定並不適當。若以血液或臟器中之鋅及鎘含量之差異性可能是一個更好的指標物。

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Studies on The Chronic Cadmium Intoxication: General Aspects

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ABSTRACT

Cadmium deeply affected the internal organs of the rats which were administered with cadmium acetate solution containing cadmium ions 100 ppm as drinking water for a long period. Especially their lung, heart, brain and thymus showed distinct atrophy ($P<0.05$-$P<0.001$). There was mainfestation of anemia, and slightly higher WBC count with lower neutrophils percentage .The effect of cadmium on the function of kidney and liver was not significant. The zinc and cadmium levels of the cadmium administered rats significantly increased as compared with those of the control group ($P<0.05$-$P<0.001$).

The above results indicated that the effect of cadmium on the rats was most distinctly manifested in the atrophy of their lung, and their kidey and liver function was not the appropriate index of intoxication in the case of chronic cadmium intoxication, whereas the high content of zinc and cadmium in their blood and other organs might be useful for reference.

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