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Pharmacological and Toxicological Investigations of Cesium

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PINSKY, C AND R. BOSE *Pharmacological and toxicological investigations of cesium.* PHARMACOL BIOCHEM BEHAV **21**: Suppl 1, 17–23, 1984 —Cesium, a mineral resource abundantly present in Manitoba with important existing and potential industrial applications was investigated to study its effects on biological systems Several rodent models of pharmacological activities were utilized The profile that emerged indicated that cesium is only moderately toxic and exerts salubrious effects which could be gainfully investigated for application in the treatment of certain psychological disorders and some tumors Its conjunction with existing pharmacological agents for these two types of disorders could yield a pharmacologically active yet less toxic therapeutic combination

Cesium Cesium CAR attenuation Cesium antipsychotic synergism Antitumor Positron-emitting cesium Radiodetection Cesium glucose interaction Cesium magnesium interaction PIKXE cesium determination Cesium vasopressor activity Cesium catecholamine release

CESIUM, the "blue" element, was discovered in 1860 by Kirchoff and Bunsen and belongs, with sodium, potassium and lithium, to the biologically-significant periodic Group Ia of alkali earth elements.

Cesium is present in pollucite, epidolytes, granite-like bedrock and chalky deposits in vast quantities in the crust of the earth. In economic terms, a conservative estimate would indicate that deposits around Bernic Lake, Manitoba, contain some 68% of the world supply of cesium [7,11]. Cesium is presently used in electronic industries (photoelectric cells, high energy lasers [24,25], atomic-resonance clocks, fluorescent screens and vacuum tubes). There is a strong likelihood of its being utilized on a massive scale in the magnetohydrodynamic generation of energy [1].

We were concerned about the possible toxic effects of cesium on miners and others who might come in contact with this element, hence we proceeded to investigate its biological effects. An early edition of the Dispensatory of the U S. A. contains a reference to clinical use of cesium salts in epilepsy [22] and cites even earlier studies dating back to 1888 Several more recent studies have reported various effects of cesium salts on different animal models. Vadrot *et al* [26] have reviewed the relative toxicity of various compounds of cesium, its effects on the neuromuscular junction, its possible CNS antidepressant activity and its effects on several tumors The present account given below summarizes most of our own studies undertaken over the last few years to explore the effects of cesium on biological systems.

GENERAL SCREENING

Behavioral Observations and Toxicity

Graded doses of CsCl (1.25 to 20.0 mEq/kg, via intraperitoneal (IP) injection) were administered to groups of albino Swiss-Webster mice The animals were observed for 15 min while changes in their general behavioral elements (locomotion, rearing-up, grooming, sniffing, teeth chatter, urination, salivation and defecation) were noted.

The incidence of death was assessed in these animals 24 hr after CsCl administration. Median lethal dose was estimated by the method of Miller and Tainter [19]. The acute LD50 of cesium chloride in mice by the intraperitoneal route was estimated to be 10.0±0.84 mEq Cs^+/kg. Before death the animals exhibited respiratory distress followed by severe whole body clonic and tonic convulsions. All mice drooled, those receiving the higher doses (10 and 20 mEq Cs^+/kg, IP) had copious salivation almost resembling vomiting, the latter being uncommon in rodents. Urination showed inconsistent increases with cesium administration while fecal pellets were soft, ill-formed and malodorous. The higher doses also produced piloerection in about one-third of mice so treated. There was an initial transient phase of hyperexcitability following cesium injection at all doses studied. This was replaced within minutes by varying degrees of dose-related CNS depression, reflected as reduction in spontaneous locomotor activity and disinclination to move even on being touched, thus demonstrating reduced reactivity. The mice were awake with unaffected righting reflex and responding to painful stimuli such as pressure applied to tail or joints. Animals seemed generally to tolerate doses under 10 0 mEq/kg without much discomfort, hence we selected doses of 5.0 mEq/kg or lower in subsequent studies. Suppression of locomotor activity was significantly correlated with the dose of cesium and the median effective suppressant dose was estimated to be 2 7 mEq/kg.

Interaction With CNS-active Drugs

Mice were pretreated with CsCl (5.0 mEq/kg/day×7 days, IP) and then given pentobarbital (30.0 or 50.0 mg/kg, IP) or

TABLE 1

INTERACTION OF CsCl WITH D-AMPHETAMINE AND PENTOBARBITAL IN MICE

Pretreatment*	Amphetamine† dosage	N	Mortality Proportion animals dead	p‡	Pentobarbital† dosage	N	Sleeping time mean ± S E min	p§
NaCl	20 0	10	6/10		30 0	10	4 ± 1 6	
CsCl	20 0	10	3/10	N S	30 0	8	27 ± 3 0	0 001
NaCl	40 0	10	10/10		50 0	10	50 ± 5 0	
CsCl	40 0	10	4/10	0 025	50 0	10	87 ± 6 9	0 001

*5 0 mEq/kg da^{-1} IP×7 days, †mg/kg IP, significance of difference from concurrent saline controls (N S =not significant) ‡Chi-square test with Yates' correction, §Student's t-test

Bose and Pinsky (1984 in press) courtesy of Springer-Verlag

TABLE 2

EFFECTS OF CESIUM ION ON CONDITIONED AVOIDANCE IN RATS

Treatment×No of Injections IP	N	Total Trials	Successful Avoidance Responses	p
Saline×4	8	40	39	
CsCl 3 0 mEq kg^{-1}×4	8	40	31	<0 02*
Saline×7	4	20	19	
CsCl 3 0 mEq kg^{-1}×7	4	20	16	†

*Different from concurrent saline controls (chi-square)

†No significant difference from concurrent controls

Bose and Pinsky ([2] p 869), Courtesy of Ankho International

TABLE 3

EFFECTS OF CESIUM ION ON CONDITIONED AVOIDANCE RESPONDING IN MICE

Treatment×No of Injections IP	N	Total Trials	Successful Avoidance Responses	p
Saline×7	9	45	45	
CsCl 5 0 mEq kg^{-1}×7	15	75	46	<0 001*
Saline×14	8	40	40	
CsCl 5 0 mEq kg^{-1}×14	9	45	17	<0 001*

*Different from concurrent saline controls (chi-square)

Bose and Pinsky ([2] p 870), Courtesy of Ankho International

d-amphetamine sulfate (20 0 or 40 0 mg/kg, IP). Pentobarbital hypnosis was significantly potentiated (p<0 001, Table 1) whereas amphetamine-induced aggregation toxicity was significantly attenuated (Table 1). This profile is similar to that shown by antidopaminergic antipsychotic agents [6, 12, 13] We next proceeded to screen the effect of cesium on conditioned avoidance, a phenomenon which is known to be a sensitive and specific correlational model for screening of antidopaminergic antipsychotic agents [5]

Conditioned Avoidance Response (CAR), Catalepsy

Mice and rats were trained to avoid electroshock on a pole-climbing CAR paradigm [2] They then received CsCl (rats, 3 0 mEq/kg/day up to 7 injections, mice, 5 0 mEq/kg/day up to 14 injections) A significant attenuation of CAR was observed in rats after four injections (Table 2) and in mice after 7 or 14 injections, when compared with corresponding saline-treated animals (Table 3) We noticed also a significantly lowered rate of acquisition of CAR in cesium-treated mice (5 0 mEq/kg, IP) Moreover, a subeffective dose of CsCl (1 0 mEq/kg×3 daily injections, IP) synergised with chlorpromazine (0.5 mg/kg, IP) to a significant degree in attenuating CAR (Table 4). A similar and more pronounced synergistic effect was observed also with haloperidol (Table 5). We interpret these findings in sum as indicative of a suppressant effect of cesium chloride on central dopaminergic transmission One possible mechanism by which this could take place is by inhibition of dopamine release, as suggested by the findings of Rastogi *et al* [21], perhaps in a fashion similar to that produced by gamma-hydroxybutyric acid [23]

Mice received CsCl (2 5 or 5 0 mEq/kg/day, IP for up to 31 days) Control mice received equivolume injections of normal saline for equal durations They received chlorpromazine·HCl (CPZ, 0 2 mg/kg, IP) after 15 and 31 injections of either CsCl or NaCl Catalepsy was tested by lattice immobility test (summative duration of total immobility on vertical wire grid out of a total stay time of 5 min) and by pedestal-clinging test (forepaws placed on a 3 cm high cork pedestal, total duration of stay on the pedestal out of a 5-min testing period) Table 6 shows that 0 2 mg/kg CPZ, ineffective by itself, can potentiate the effects of 15 once-daily injections of CsCl at 2 5 and at 5 0 mEq/kg/day in the lattice-immobility test for catalepsy It failed, however, to potentiate 31 similar injections of CsCl Table 7 indicates that the pedestal test for catalepsy is sensitive to a different dose range of the antipsychotic drugs In this test the same dose of CPZ was effective by itself after 31 injections of saline CPZ potentiated 15 once-daily injections of CsCl at 5 0 mEq/kg/day, IP but not at 2 5 mEq/kg/day, IP As in the lattice-immobility test, CPZ did not potentiate the effect of 31 injections of CsCl at either of the two doses tested by us on pedestal test In sum, CPZ appears to potentiate the

TABLE 4

MUTUAL SYNERGISM BETWEEN CESIUM CHLORIDE AND CPZ

Group	Pretreatment*	CPZ Treatments mg/kg†	N	CPZ Effect on CAR f_M Scores, % Attenuation mean ± S E ‡
A	saline	0 1	8	47 ± 10 0
B	saline	0 5	8	65 ± 6 1
C	CsCl	0 1	6	69 ± 7 7
D	CsCl	0 5	6	90 ± 3 6§

*Pretreatment consisted of three IP injections, given once daily for three days, of either isotonic saline or CsCl at 1 0 mEq/kg

†CPZ treatment was one IP injection at dose shown, administered 24 hr after last injection of saline or of CsCl Details in text

‡Assessed as % attenuation of f_M scores relative to those found just after third pretreatment injection with saline or CsCl Details in text

§The mean f_M values in this group are significantly different from those in all other groups ($p<0$ 05, Student's unpaired t-test) Note that mean scores for Groups A and B are not significantly different from each other

Bose and Pinsky ([3] p 325), courtesy of PJD Publications Ltd , NY

cataleptogenic effect of repeated injections of CsCl, but this synergism appears to wear off with multiple injections of CsCl

Effect of Cesium on Mouse Blood Pressure (BP)

Mice weighing between 30–40 g were anesthetized with urethane (1 5 g/kg, IP) The abdominal aorta was cannulated via 5 cm of P50 polyethylene tubing and connected to a Statham P23Db low-volume displacement pressure transducer The mean BP was recorded and measured off a chart recorder Mesenteric instillation of CsCl at 0 025 to 0.2 mEq/ml produced a consistent, short-lived dose-related rise in BP. Four such administrations of CsCl (0 075 mEq/ml) resulted in the development of complete tolerance to the response (tachyphylaxis) Furthermore, the rise in BP was partially prevented (67 8±16 57% reduction in vasopressor effect) by pretreatment with the ganglionic-blocking agent mecamylamine (2 5 mg/kg, subcutaneous), or by bilateral adrenalectomy Taken together these results are consistent with a stimulant effect of cesium chloride on preganglionic cholinergic nerve fibres Such an effect could explain also the autonomic changes (salivation, piloerection, urination, diarrhoea) observed earlier

Effect of Glucose and Magnesium on CsCl-Induced Convulsions

CsCl was administered in a convulsion-producing dose (8.22 mEq/kg, IP). The latencies to appearance of anoxia, convulsion and death after injection of CsCl were noted Also noted were incidence of convulsions and death in the group Other groups of mice were pretreated with a range of doses of d-glucose, l-glucose, osmotic agents (mannitol, urea) or magnesium chloride before being challenged with CsCl at the same convulsant dose The above-mentioned latencies and incidences were recorded and compared with data from mice receiving only CsCl Moderate concentrations of d-glucose, calculated approximately to double plasma glucose levels, significantly prolonged the latencies to convulsions and death. l-Glucose, used as an osmotic and metabolic control, was inactive. We were intrigued on finding that in very high concentrations l-glucose was a much more effective anticonvulsant than was d-glucose; this phenomenon might very well merit further study. Other osmoactive agents were marginally effective (Table 8). Magnesium chloride at 0 5 g/kg, IP prevented cesium-provoked gasping, convulsions and death, to a significant degree. In contrast, the convulsive dose of CsCl did not significantly shorten the sleeping time produced by magnesium in treated mice, it in fact increased it noticeably although not to a statistically-significant level. These latter results suggest a separation between magnesium hypnosis and its protective effect against cesium convulsions.

ESTIMATION OF CESIUM IN BODY TISSUES BY THE PROTON-INDUCED K X-RAY EMISSION (PIKXE) TECHNIQUE

While carrying out pharmacological studies we were concerned about the accumulation of CsCl in the various body tissues This was of importance not only in correlating levels with pharmacotoxicological effects but also in predicting the cesium levels to be expected in persons exposed to the element at different stages of its processing. With the collaboration of the Cyclotron Laboratory, University of Manitoba, we prepared tissue samples for determination of cesium by the PIKXE technique ([14], we have contrived the acronym PIKXE to emphasize the importance of measuring K x-ray spectra, as opposed to the lower energy L x-ray spectra, in this work). A group of mice received 28 once-daily injections of CsCl, 5 0 mEq/kg/day, IP. Small numbers of mice were drawn after 1, 3, 14, 21 and 28 injections (to monitor accumulation) and also at 7, 14, 21 and 28 days after the final (28th) injection (to monitor washout). Animals were decapitated and carotid arterial blood and tissue samples of brain, liver, lung, ileum and skeletal muscle were collected The brain was further dissected into three portions—forebrain, midbrain and hindbrain These tissues were digested overnight with concentrated nitric acid (ARISTAR, B D H , 1·3 w/w) containing dysprosium·HCl (842 microgram per ml) as internal marker dopant. The resulting solution was applied to mylar film (8C, 80-microinch average thickness, a gift from Dupont de Nemours) The cesium/dysprosium ratios, and thus cesium content, was estimated by the PIKXE technique [20]. All tissues accumulated cesium over the period of administration, with a high to low order of skeletal muscle, ileum, brain, liver, lung and blood (Table 9) Blood levels were fairly steady over the period of administration, suggesting a rapid transfer of cesium from blood to tissue compartments. The washout of CsCl was fairly similar in all the tissues studied, the period required to reach half-concentration after 28 injections of CsCl ranged between 3.25 and 4.5 days In most tissues (exceptions being blood, cerebellum, medulla oblongata and ileum) the levels of cesium increased up to the 14th injection and declined thereafter, suggesting a dynamic equilibrium between the influx and efflux of CsCl in these tissues with the latter becoming more active than the former over the observed time course Interestingly, such a situation will tend *per se* to prevent the maximum levels of CsCl from rising above toxic concentrations.

TABLE 5

MUTUAL SYNERGISM BETWEEN CESIUM CHLORIDE AND HALOPERIDOL

Treatment	Haloperidol Effect*		
	Number of IP Saline or CsCl Injections		
	1	2	3
	Number of IP Injections with Haloperidol†		
	1	2	3
Isotonic saline	87 ± 27	57 ± 15	58 ± 13
	n=14	n=14	n=14
CsCl, mEq/kg/day IP			
1 0	61 ± 15	75 ± 8	62 ± 10
	n=6	n=6	n=6
2 5	27 ± 10‡	51 ± 19	45 ± 11
	n=7	n=7	n=6
5 0	36 ± 13	13 ± 4§	20 ± 7§
	n=6	n=6	n=6

*Expressed as percentages of pre-haloperidol f_M scores obtained 24 hr before listed injection of haloperidol

†Haloperidol administered at 50 μg/kg IP Details in text

‡Essentially statistically-different from corresponding saline-treated group, see text

§Statistically-different from corresponding saline group, $p<0$ 05, Student's unpaired t-test

Bose and Pinsky ([3] p 326), courtesy of PJD Publications Ltd , NY

TABLE 6

LATTICE-IMMOBILITY TEST FOR CATALEPTIC BEHAVIOR

Days of Treatment	Mean Immobility Time ± S E , sec* One-Daily Treatment		
		CsCl, mEq/kg/day IP	
	Saline	2 5	5 0
1	82 ± 21 6	109 ± 23 2	140 ± 29 1
7	102 ± 27 1	55 ± 19 4	115 ± 23 6
14	108 ± 28 0	110 ± 17 8	144 ± 21 5
15 (+CPZ)*	98 ± 15 0	161 ± 18 5†	203 ± 23 9‡
26	93 ± 18 5	120 ± 29 5	156 ± 21 8
31 (+CPZ)†	94 ± 32 3	150 ± 30 9	183 ± 28 1

(n=5 for all groups, except for two instances of n=6 and two of n=4)

*Over 5-min observation period

†Chlorpromazine HCl, 0 2 mg/kg IP, given at 1 hr after IP injection of either saline or CsCl

‡Significantly different ($p<0$ 05, Student's unpaired t-test) from corresponding saline-treated group

TABLE 7

PEDESTAL-CLINGING TEST FOR CATALEPTIC BEHAVIOR

Days of Treatment	Mean Immobility Time ± S E , sec* One-Daily Treatment		
		CsCl, mEq/kg/day IP	
	Saline	2 5	5 0
1	24 ± 2 9	18 ± 7 9	23 ± 3 8
7	35 ± 9 4	43 ± 14 3	73 ± 19 1
14	28 ± 9 6	58 ± 17 5	93 ± 26 3
15 (+CPZ)†	45 ± 8 5	61 ± 12 3	144 ± 40 6‡
26	31 ± 5 6¶	29 ± 8 8	58 ± 13 0
31 (+CPZ)†	55 ± 5 4§	55 ± 7 5	128 ± 45 0

(n=5 for all groups, except for two instances of n=6 and two of n=4)

*Over 5-min observation period

†Chlorpromazine HCl, 0 2 mg/kg IP, given at 1 hr after IP injection of either saline or CsCl

‡Significantly different ($p<0$ 05, Student's t-test) from corresponding saline control

§Significantly different (as above) from results at (¶)

TABLE 8

EFFECTS OF MAGNESIUM, ISOMERS OF GLUCOSE AND SOME OSMOACTIVE AGENTS ON SLEEPING TIME AND CsCl-INDUCED TOXICITY

Group	Pretreatment dose g/kg IP	CsCl mEq/kg IP	Sleeping Time mean ± S E sec	Gasping (Anoxia) Incidence	Gasping (Anoxia) Latency mean ± S E sec	Convulsions Incidence	Convulsions Latency mean ± S E sec	Death Incidence	Death Latency mean ± S E sec
A	—	8 2	—	7/8	318 ± 17 1	7/8	1139 ± 239.8	4/8	1184 ± 223 2
B	$MgCl_2$ 0 5	—	182 ± 68.0		—		—		—
C	$MgCl_2$ 0 5	8 2	268 ± 91 6	0/6†	>1800 ± 0‡	0/6†	>1800 ± 0	0/6	>1800 ± 0
D	d-glucose 2 0	8 2	—	8/12	992 ± 181 9‡	6/12	3995 ± 665.5‡	6/12	4221 ± 7745
E	l-glucose 2 0	8 2	—	2/7	1383 ± 347‡	0/7	>24 hr	0/7	>24 hr
F	mannitol 0 13	8 2	—	3/8	383 ± 23 5	5/8	834 ± 128 5	5/8	885 ± 125 3
G	mannitol 0 4	8 2	—	7/8	530 ± 86 3*	5/8	877 ± 129 2	5/8	957 ± 124 5
H	urea 0 4	8 2	—	6/7	302 ± 17 6	7/7	385 ± 12 6‡	7/7	464 ± 27 1‡
I	urea 1 2	8 2	—	3/8	323 ± 25 9	7/7	323 ± 125 3‡	7/7	429 ± 92 5‡

p values—*<0 05, †<0 02, ‡<0 001, Statistically different from corresponding parameter of group A

TABLE 9

TISSUE LEVELS OF CsCl AS DETERMINED BY PIKXE AFTER TREATMENT WITH CsCl (5 0 mEq/kg IP/DAY)

Number of CsCl Injections	Mice Sacrificed After Last Injection	Cesium Content in mEq/kg Wet Tissue: Cerebellum and Medulla Oblongata	Midbrain Diencephalon Striatum	Remaining Forebrain	Blood	Lung	Liver	Ileum	Skeletal Muscle
1	24 hr	48±24 9	77±34 5	157±8 4	103±12 6	383±38 3	326±50 0	352±97 8	156±26 4
3	24 hr	503±7 9	417±39 5	561±51 6	227±14 1	704±83 7	1082±115 4	1055±90 5	777±103 6
14	24 hr	572*	1394*	1759*	215*	971*	1350±28 9	1849±142 5	1787±692 3
21	24 hr	1041±74 3	1001±91 5	990±77 6	268±31 6	781±53 8	1132±80 3	1055±91	1141±208 6
28	24 hr	679±74 8	596±22 6	571±72 4	236±47 6	822±4	772±85 9	1570±1335 5	1957 5±1352 5
28	7 days	219±42 8	217±42	203±86 9	44±8 5	197±29 5	158±25 3	217±41 3	194±55 6
28	14 days	247±215 1	62±18 7	77±12 7	10±6	92±34	58±15 8	43±13 7	144±50
28	21 days	1 0*	17 5*	16 5*	12±5 1	23±7 8	19±10 6	22±7 1	46±16 2
28	28 days	30*	27 4±21 7	15±5 8	20±7 1	8±5 3	2 0*	11±4 9	11 5±6 9

*n=2, rest n=4 to 8

CESIUM AND TUMOR TISSUES

There had been some reports in literature about the effects of cesium on tumors [16, 18, 27]. There were also reports indicating a certain degree of affinity shown by some tumors for accumulating cesium and the applicability of this property of tumors for assessing their response to chemotherapeutic intervention and thus the prognosis [9]. We were particularly drawn by these latter findings which indicated a possible use of cesium in diagnosis of tumors by exploiting their preferential affinity for cesium.

Antitumor Effect

Two different kinds of tumors were studied in our laboratory, namely. MT296 mammary adenocarcinoma in BALB/c mice and benzo(a)pyrene (BZP)-induced epithelial carcinoma in Swiss-Webster mice.

MT296 Tumor

MT296 tumor cells were plated subcutaneously into BALB/c mice according to the technique of Henderson [10] The mice then received CsCl (0.5 to 3.0 mEq Cs^+/kg/day IP

for up to 42 days) Cesium-treated mice showed significantly less tumor growth than corresponding controls They showed, however, significantly higher lymphoid growth In fact, tumor growth was negatively correlated with lymphoid growth to a significant degree

BZP-Induced Skin Cancer

Swiss-Webster mice received injections of either saline or CsCl (0 5 to 3 0 mEq/kg/day, IP) From the 9th day onwards the depilated skin on the backs of these animals received topical application of 30 μl BZP, 0 5% in chloroform, once daily This was followed by application of 30 μl of oleic acid (as tumor promoter, Dalecka *et al* , unpublished) per application every other day for a total of five applications Tumors were assessed by semiquantitative visual scoring on days 47 and day 52 The animals were then killed and samples were subjected to histological examination. Such prolonged treatments with cesium did not cause any death in the treated group There was a definite dose-related reduction in mean tumor size in vivo. Mean tumor latency in all cesium-treated groups was numerically greater than that in the no treatment and saline control groups, tumor latency in the group treated with CsCl at 0 5 mEq/kg was longer than that in either of the two control groups

Radiodetection of Tumors by Positron-Emitting Cesium

A positron-emitting isotope of cesium (^{132}Cs, $t(1/2)$=6 5 days) was prepared by our collaborators from the Cyclotron Laboratory, University of Manitoba, utilizing the ^{133}Cs(p,pn)^{132}Cs reaction [8] This was injected at a dose of 4 6 mEq/kg, IP into BALB/c mice bearing MT296 tumors Two coaxial coincident gamma detectors were positioned over the tumor region in some mice and over the head region in others The head region was chosen for comparison because the region is highly vascular and the brain does not avidly take up cesium, thus providing a fairly reliable estimate of background levels of cesium in blood After the radioactive uptake had reached a plateau, positron emission was estimated in the other region of the same animal (head in case of dynamic tumor-uptake measurement and tumor in case of head-uptake measurement) Thereafter, the animals were killed and their brain, liver, tumor, skeletal muscle, skin and fascia samples were dissected and the gamma emission (4 11 MeV) was estimated *in vitro*

Our results showed that a single moderate dose of cesium (approximately 500 nanocuries per mouse) is taken up by mouse mammary tumor tissue to an extent that permits noninvasive extracorporeal monitoring and region-selective identification of tumor mass within a few minutes after administration of the positron-emitting ^{132}Cs [15] In studies on excised tissues we found that the uptake rate for cesium was higher in our model of tumor tissue than in brain, skeletal muscle and skin, while being less than that found in small intestine and kidney

A separate experiment was conducted to test whether such uptake was ion-specific and also its degree of dependence on number of administrations. BALB/c mice bearing MT296 mammary tumors were administered with stable CsCl or stable RbCl (both at 3.0 mEq/kg/day×7 injections, IP) Twenty-four hours after the seventh injection, the mice were killed and their tumor, brain, liver and skeletal muscle tissues were excised and the tissue levels of Cs and Rb were measured by the PIKXE technique We found that cesium accumulated to a greater extent than rubidium in tumor, brain and skeletal muscle However, liver appeared not to discriminate significantly between cesium and rubidium The tumor tissue, as with acute administration, accumulated significantly greater amounts of cesium than did either liver or brain. After a single injection the tumor tissue accumulated more cesium than did skeletal muscle, but after seven successive once daily injections, there was no significant difference between the total cesium uptake in the two tissues These regimen-related differences in tissue uptake may have been due to a slowly-developed saturation of cellular selective uptake mechanisms, evident only after several days of continual exposure to the cesium ion

CONCLUDING REMARKS

Our experience with cesium indicates that it is not very toxic in moderate doses (5 0 mEq/kg/day or lower IP in mice, up to 120 days of daily administration). Cesium appears to be much better tolerated than its neighbour lithium which is known to cause severe toxicity when blood levels exceed 1 8 mEq/L Cesium has marked pharmacological actions on the central nervous system and on malignant tissue The decrease in locomotor activity, blockade of conditioned avoidance response and synergism with antipsychotic agents indicates a possible therapeutic synergism with antimanic and antischizophrenic dopamine antagonists This is more so because probable therapeutic summation of these drugs with cesium, as indicated by blockade of CAR, is considerably more than that of untoward and toxic effects as indicated by a less prominent synergism of cataleptic effect The exact mechanism of such synergism between cesium and a very different chemical class of drugs, namely antipsychotic, antidopaminergic agents, is not known Excessive neuronal release leading to depletion of the transmitter, with consequent diminished release, is one possibility Our experiments on mouse blood pressure indicated that, at least in the periphery, cesium might induce the release of catecholamines This would explain the cesium-provoked rise in BP and the development of tachyphylaxis to the vasopressor effect, the latter being attributed to transmitter depletion A similar effect on central dopaminergic neurons would explain not only the synergism of cesium with antidopaminergic drugs but also the initial excitation seen with cesium treatment This excitation would be due to a transient increase of dopamine release at central dopaminergic nerve terminals Such release would be reflected as an increase in turnover of dopamine and in levels of DA metabolites, as has been shown by other workers [21] This postulated biphasic action of cesium on the release of dopamine and possibly of other catecholamines could reconcile reports from different laboratories where only one or another aspect of cesium effects on motor behavior may have been emphasized [17]

Cesium appears to be taken up preferentially by MT296 mammary tumor, especially after multiple administrations It also exerts antitumor effects on BZP-induced skin carcinoma and MT296 mammary adenocarcinoma Considering the low toxicity of cesium chloride, and our ability to antagonize its most severe toxicity with isomers of glucose, it would be of interest to study the possible synergism between cesium and anticancer drugs currently being used in the therapy of malignancies A therapeutic combination with low toxicity might be obtained thereby Also, further exploration of the applicability of positron-emitting isotopes of cesium in diagnosing small internal malignancies could be beneficial, and would prove to be another unique medical use of this fascinating element

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