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Lithium Levels in Monkey and Human Brain After Chronic, Therapeutic, Oral Dosage[1]

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SPIRTES, M. A. *Lithium levels in monkey and human brain after chronic, therapeutic, oral dosage.* PHARMAC. BIOCHEM. BEHAV. 5(2) 143–147, 1976. – Lithium levels in 32 different brain areas of 5 macacus rhesus receiving 13 mg/kg daily orally of lithium carbonate for 3–6 weeks are reported. These vary from 0.36 ± 0.08 to 0.82 + 0.35 meq/kg. Levels have also been determined for most of the tissues and organs of these monkeys. They vary from 0.25 meq/kg for the carotid artery to 13.71 and 13.61 meq/liter or kg for urine or toe nails. The manic-depressive patient involved died of acute alcoholic and darvon toxicity. His whole blood level of Li was 0.86 meq/L. Two of the 16 brain levels investigated amounted to 1.49 and 1.21 meq/kg (retrosplenial cingulate gyrus and caudate nucleus). Others were as low as 0.09 meq/kg (brain stem). Li levels in a number of organs of this patient were similar to those in monkeys. Possible conclusions from these values are discussed.

Lithium levels Manic depressive syndrome Brain Peripheral organs

THERAPEUTICALLY, lithium (Li) salts have been used very extensively during the last 20 years for the manic-depressive syndrome. There have been no extensive reports, however, of lithium levels in various parts of the brain and other organs of monkeys or man after ingestion of amounts of Li salts roughly equivalent to therapeutic sustaining doses in man. This report presents such figures, the data having been gathered from experiments with 5 monkeys and 1 man, a manic-depressive, who committed suicide while on a maintenance dose of 1200 mg/day of Li Carbonate. In the brains of monkeys there is a 2.3 fold spread in values and all are lower than in the blood serum or cells. In the case of the one man, there is a much larger spread of Li values in the brain and in two areas the Li levels are much higher than in whole blood. Unfortunately serum and RBC could not be obtained in this case, only highly hemolyzed, clotted whole blood. In monkeys, the ratio Erythrocyte Li/Serum Li was found to be 1.44. This is higher than the reported values of 0.4 and 0.8 for man. A discussion of the results is included.

MATERIALS AND METHOD

Chemical and Apparatus

All chemicals used, organic or inorganic including Li_2CO_3, were either of A.C.S. or C.P. grade, or the purest available commercially. For Li_2CO_3 standards, the reference standard of the Fisher Scientific Co. was purchased and diluted as needed. Na^+ and K^+ standards were made from commercial A.C.S. grade salts. Heparin, as the ammonium salt, was purchased from the American Hospital Supply Co., Evanston, Ill. 60201. It contained 1000 USP units per ml. 100 units were used for 10 ml of blood with mixing. Li^+, Na^+ and K^+ determinations were carried out with the Perkin-Elmer atomic absorption spectrophotometer Model No. 303 with separate Li^+, Na^+ and K^+ lamps. Glass-distilled H_2O was utilized to make up all solutions and during all determinations. The ultrasonic apparatus used was purchased from Heat Systems Inc. (Model No. W – 185). All pipettes and glassware were made of pyrex grade glass and were thoroughly washed first in soapy H_2O, then in concentrated H_2SO_4 followed by 10 washings in distilled H_2O from a Barnstead still and 10 further washings in glass-distilled H_2O. Dry ice was purchased commercially when needed.

Procedural Technique for Treating Animals with Li_2CO_3, for Sacrifice and Obtaining Organ Samples for Li Determinations

Young male, macacus rhesus monkeys weighing 6–10 kg were daily fed 13 mg Li_2CO_3 divided into 3 doses. Each dose was imbedded in a portion of banana or an orange or placed in a pellet of monkey chow into which was bored a hole, the Li_2CO_3 buried in it and covered with a bit of wetted monkey chow. The animals were not fed their usual monkey chow and H_2O ad lib until they had finished the prepared doses of lithium. Every week the method of

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preparing the Li doses was changed since the monkeys apparently recognized the prepared dosages quickly and spat out the Li-containing fruit or pellet when the diener's back was turned. When necessary and at the time of sacrifice, the animals were lightly anesthetized and 3 ml of blood removed for Li^+ determinations. At the time of sacrifice as much IV blood as possible was first obtained from each animal, its chest opened, and an opening was first cut in the left ventricle into which the narrowed end of a piece of glass tubing was immediately placed and connected to a perfusion fluid glass receptacle holding 1 liter of 0.25 Molar sucrose (pH 7.4 in. 0.01M tris buffer). Another opening was made in the left auricle by snipping off a piece of this chamber, after which the perfusion was started. The perfusion fluid was kept cold and 5 liters allowed to pass through the cardiovascular system of the animal. With a successful infusion it could be seen that the liver became tan in color, and the spleen very pale from its original venous blue color. At the conclusion of infusion, the fluid exiting from the left auricle should be colorless. Samples of all body organs were then removed (50–150 mg of tissue), blotted on absorbent paper, rinsed several times with glass-distilled H_2O, blotted again and put into small, labelled glass vials which were immediately placed on dry-ice until frozen. Special precautions were taken for skin, hair, nails and g.i. tract samples. Here, more copious washings were done and, in the case of skin, hair and nails, initial scrubbings with a brush (even under the nails) was carried out to prevent contamination of these organs with the Li of the diet.

Following the removal of as many specimens as possible from body organs (this lasted about 1 hr), the skull was exposed, scraped free of tissue and cut open with a dental disc drill in such a manner that the roof could be removed and the brain exposed and removed as a whole. This was then dissected into the various regions listed and specimens varying from as small as 10 mg to 250 mg removed, placed in bottles with screw caps and kept on ice until weighed. The glass vial and organ sample were weighed together, the sample removed, the vial alone dried carefully and weighed again. The difference in the two weights comprised the weight of the organ sample. The latter was cut up as fine as possible and placed in a 12 ml graduated heavy duty conical test tube to which was added 1 ml of concentrated HNO_3, A.C.S. grade, in the case of the peripheral organs. These tubes were placed in an electrically heated sand bath until the tissue was digested and the tubes were dry. With slow heating, the color of the contents went from black to colorless or straw yellow. A glass bead was included to prevent bumping. If the contents were not colorless when dry, then 1 ml of H_2O was added to the digestion continued until the process was finished (24–48 hr). The tube was then brought up to a known volume with glass-distilled H_2O and agitated for 60 sec with the aid of the microtip of the sonication apparatus while the tube was in cold water bath (0–4°C) to prevent boiling. Following a short period of hand agitation, the sample was sent through the Perkin-Elmer Atomic Absorption spectrophotometer equipped with a lithium lamp. Standard reference standards of 0.05, 1.0 and 1.5 ppm (parts per million) were used. In the case of the brain samples, 2–3 ml of distilled H_2O was added to each sample and a similar agitation process as mentioned above with ultrasonication was carried out, following which the samples were directly sent through the Perkin-Elmer apparatus without previous digestion. A special wide burner, Model No. 303-0202, was used to prevent clogging by protein in the case of the brain samples. This burner was frequently inspected and cleaned once or twice weekly with a razor blade as instructed.

RESULTS

Table 1 records the values for lithium levels in various areas of the brain after the monkeys were fed lithium carbonate daily at a dose of 13 mg/kg for a period of 3–6 weeks. Because only 5 animals were used and the feeding period was variable there was considerable spread in the values for each region. In order to appreciate this spread, standard deviations rather than standard error of the mean terms were calculated.

TABLE 1

LI LEVELS IN DIFFERENT BRAIN AREAS OF NORMAL MALE PRIMATES* AFTER BEING ORALLY FED Li_2CO_3 FOR 3–6 WEEKS

Average values between 0.6-0.82 meq/kg ± standard deviation from the mean	
Anterior thalamus	0.82 ± 0.35
Head, caudate nucleus	0.65 ± 0.17
Fornix	0.61 ± 0.17
Cingulum	0.60 ± 0.47
Average values between 0.50-0.60 meq/kg ± standard deviation	
Putamen	0.59 ± 0.16
Posterior hippocampus	0.58 ± 0.22
Corpus callosum	0.56 ± 0.13
Posterior thalamus	0.56 ± 0.27
Anterior hippocampus	0.56 ± 0.17
Olfactory tract	0.52 ± 0.24
Half brain (average brain value)	0.50 ± 0.10
Subcallosal cingulate	0.50 ± 0.13
Average values between 0.40-0.50 meq/kg ± standard deviation	
Amygdala	0.48 ± 0.14
Retrosplenial Cortex	0.46 ± 0.12
Midbrain	0.46 ± 0.12
Sensory Cortex	0.46 ± 0.19
Anterior Hypothalamus	0.46 ± 0.22
Pons	0.45 ± 0.09
Motor Cortex	0.45 ± 0.15
Medulla	0.45 ± 0.13
Posterior hypothalamus	0.44 ± 0.09
Cortex tip, ventral temporal lobe	0.44 ± 0.13
Cingulate gyrus	0.43 ± 0.08
Cortex tip, occipital pole	0.43 ± 0.16
Globus pallidus	0.41 ± 0.10
Uncus	0.41 ± 0.10
Average values under 0.4 meq/kg ± standard deviation	
Spinal cord	0.39 ± 0.12
Cerebellum	0.39 ± 0.11
Tip of temporal lobe	0.37 ± 0.11
Optic chiasm	0.37 ± 0.12
Cortex tip, frontal pole	0.36 ± 0.08

Average blood plasma—1.0 meq/liter. All Li values are the average meq/kg or liter of 5 monkeys.

*Macacus rhesus monkeys: 5 adult males; average weight 7.5 kg. Li_2CO_3 dosage: 13 mg/kg/day orally-divided into 3 daily portions for 3–6 weeks.

Roughly there is about a 130% spread among the values from the 32 different brain areas examined. These have been divided into 4 groups including a group of the lowest under 0.4 meq/kg, two intermediary groups and the highest, the later from 0.6–0.82 meq/kg. It is to be noted

that the average Li level in the heparinized blood plasma of these 5 monkeys was normalized to 1.0 meq/liter. Actually the range was from 0.9–1.2 meq/liter. Other Li levels in all organs, including the brain areas, were corrected for this normalization. Table 2 consists of a critical evaluation of the brain Li levels found, using the Duncan Multiple (new) Range Test [1]. All 32 monkey brain regions investigated are listed vertically against 9 brain areas with the highest Li levels listed horizontally. p values of 0.05 or less are considered significant. This allows for a comparison of the brain regions showing the nine highest Li levels with all the 32 brain regions investigated. It can be seen that there is no significant difference in Li levels among each other between the last twenty-three brain levels listed vertically. Also evident is the fact that the Li level in the anterior thalamus differs significantly from that of all other brain regions. The Li level in the head of the caudate nucleus differs significantly from the levels in all brain regions listed vertically from the amygdala downwards. Similarly the Li levels of the other brain regions listed horizontally differ from those seen vertically. Table 3 lists the lithium concentrations of roughly 60 organs. Because the monkeys handled the doses of lithium salts when they ate the fruit in which the salts were imbedded, all exterior organs including skin, hair and especially nails were washed thoroughly or brushed carefully with a hand brush and water. In spite of these precautions, the toe nails were found to have the highest concentration of Li, 13.61 meq/kg ± 9.8; this was about the same as urine which contained 13.71 meq/liter ± 6.10. Other organs with Li concentrations over 1.0 meq/l or kg included bone, thyroid, submaxillary gland, some skin areas and some peripheral nerves. Among the organs attaining Li concentrations of 0.70 1.0 meq/kg or liter were the pituitary at 0.82, striated muscle, cornea, retina, the smooth muscle of the ileum and the right ventricle of the heart. All others ranged from 0.25 0.7 meq/kg. Liver

TABLE 2

DUNCAN MULTIPLE (NEW) RANGE TEST RESULTS PERFORMED ON LI LEVELS IN ALL BRAIN AREAS OF 5 MONKEYS

	Normalized Date								
	A.T.	C	P	F	CI	PUT	P.HIP.	CC	PT
A. Thalamus (A.T)									
Caudate (Head) (C)	0.025								
Pineal (P)	0.01								
Fornix (F)	0.01								
Cingulum (CI)	0.01								
Putamen (PUT)	0.01								
Post Hippocampus (P.HIP)	0.01								
Corpus Callosum (CC)	0.01								
Post Thalamus (PT)	0.01								
Ant Hippocampus	0.01								
Olfactory tract	0.01								
Subcallosal cing.	0.01								
Half brain	0.01								
Amygdala	0.01	0.05							
R S Cortex	0.01	0.05							
Sensory cortex	0.01	0.05							
A. Hypothalamus	0.01	0.05							
Mid brain	0.01	0.05							
Pons	0.01	0.05							
Motor cortex	0.01	0.05							
Medulla oblongata	0.01	0.05							
P. Hypothalamus	0.01	0.05	0.05	0.05					
Vent temporal Cortex	0.01	0.05	0.05	0.05					
Cingulate Gyrus	0.01	0.05	0.05	0.05					
Occipital Cortex	0.01	0.01	0.05	0.05	0.05				
Globus Pallidus	0.01	0.01	0.05	0.05	0.05	0.05	0.05		
Uncus	0.01	0.01	0.05	0.05	0.05	0.05	0.05		
Spinal Cord	0.01	0.01	0.05	0.05	0.05	0.05	0.05		
Cerebellum	0.01	0.01	0.01	0.01	0.05	0.05	0.05	0.05	0.05
Temporal tip cortex	0.01	0.01	0.01	0.01	0.01	0.05	0.05	0.05	0.05
Optic chiasm	0.01	0.01	0.01	0.01	0.01	0.01	0.05	0.05	0.05
Frontal tip cortex	0.01	0.01	0.01	0.01	0.01	0.01	0.05	0.05	0.05

*All the brain areas examined are listed vertically. The areas with the nine highest Li levels are also listed horizontally.

†Overall significant differences between Li levels in various brain areas $F = 4.09$ DF = 31, 122 $p<0.001$ found by analysis of variance. RS = retrosplenial.

‡Individual significant differences in p values for Li levels between any two areas extracted from the overall list are recorded. Duncan's multiple Range (new) Test used.

TABLE 3

LITHIUM LOCALIZATION IN NORMAL MALE PRIMATE ORGANS AFTER CHRONIC ORAL ADMINISTRATION

Macacus rhesus monkeys: 5 adult males; average weight 7.5 kg. Li_2CO_3 dosage: 13 mg/kg/day orally divided into 3 daily portions, for 3-6 weeks.

Body tissue or organ	Average meq/liter or meq/kg.	± Standard Deviation
Blood plasma*	1.00	0.00
Erythrocytes	1.44	0.15
Whole blood	1.17	0.12
Urine	13.71	5.10
Nail (toe)	13.61	9.80
Bile	3.80	1.72
Feces	3.31	2.00
Skin c̄ hair	1.93	0.83
Humerus (cortex)	1.72	0.38
Rib Bone (whole)	1.72	0.52
Thyroid	1.42	0.56
Skin c̄ hair (thigh)	1.37	0.79
Kidney (medulla)	1.26	0.42
Lens (eye)	1.26	0.33
Nerve, sciatic	1.25	0.40
Salivary gland (sub. max.)	1.17	0.25
Nerve, femoral	1.14	0.97
Nerve, brachial	1.11	0.22
Tongue epithelium	1.11	0.34
Kidney, cortex	1.02	0.33
Left ventricle	0.97	0.21
Retina	0.97	0.22
Cornea	0.94	0.54
Muscle, tongue	0.90	0.40
Skin c̄ hair (anal, sparse)	0.88	0.80
Skin, penis	0.87	0.41
Right ventricle	0.85	0.16
Pituitary	0.82	0.26
Ileum	0.78	0.64
Optic nerve	0.77	0.15
Humerus (medulla)	0.74	0.44
Esophagus	0.72	0.24
Diaphragm	0.72	0.34
Muscle, striated	0.72	0.32
Liquor, eye	0.68	0.12
Rectum	0.66	0.25
Nerve, vagus	0.65	0.27
Hair	0.61	0.10
Bladder	0.59	0.34
Spleen	0.57	0.10
Testis	0.57	0.61
Epidymis	0.55	0.23
Left auricle	0.54	0.15
Duodenum	0.54	0.20
Trachea	0.54	0.20
Salivary, parotid	0.52	0.12
Jejunum	0.52	0.17
Colon	0.52	0.16
Right auricle	0.50	0.26
Stomach	0.49	0.14
Ureter	0.48	0.09
Pancreas	0.48	0.13
Artery, femoral	0.42	0.23
Lymph node	0.39	0.17
Lung	0.38	0.16
Artery, brachial	0.36	0.10
Aorta	0.35	0.04
Vein, femoral	0.35	0.14
Dura mater	0.35	0.22
Sclera	0.34	0.16
Adrenal	0.32	0.19
Liver	0.32	0.11
Fat	0.30	0.32
Artery, carotid	0.25	0.05

*All Li values normalized to 1.00 meq/L or Kg, for blood plasma. Range of blood plasma levels originally 0.90-1.20 meq/l. c̄ = with.

and fat were among the lowest at 0.3 and 0.32 meq/kg respectively. The urinary bladder and many arteries and veins also showed very low concentrations as did the parotid salivary gland. The lithium concentrations in 17 different brain areas and 15 peripheral organs, including whole blood from a manic-depressive patient who committed suicide after taking 1200 mg lithium carbonate daily for three months, are listed in Table 4. The two highest values in the brain were found in the caudate nucleus and the retrosplenial cingulate gyrus. Whole blood from this person only attained a level of 0.86 meq/l. Again, the liver lithium concentration was very low, only 0.4 meq/kg, and the bile and bone were very high, 2.5 and 7.8 meq/kg or l. Cardiac muscle, lymphoid tissue and thyroid lithium levels were higher than blood and ranged from 1.1 1.4 meq/kg.

DISCUSSION

A number of interesting facts emerged from this study. Firstly, the ratio of Erythrocyte Li/Serum Li is 1.44 for monkeys. Erythrocyte and serum values were obtained following the addition with mixing of NH_4-heparin (100 units per 10 ml freshly drawn blood). According to Mendels [3], the above mentioned ratio was only 0.33 for normal humans, whereas manic-depressives treated with Li (presumably at much higher levels than 13 mg/kg) develop ratios of 0.56 for Li responders and 0.39 for Li non-responders. Naylor, *et al.* [4] state that the ratio of RBC Li/serum Li in a manic-depressive treated with Li was somewhat higher, namely 0.80. Unfortunately the blood of the suicide recorded in the present data and sent from Denver to New Orleans in a receptacle containing dry ice was clotted and the cells mostly hemolyzed. The whole blood Li concentration for this human was 0.86 meq/kg. His death, therefore could not have been due to an overdose of Li taken by the patient, but in all probability, to alcohol abuse plus the use of darvon.

For the monkey brains, the mean Li concentrations varied from 0.36 ± 0.08 to 0.82 ± 0.35 (or by a factor of 2.3) whereas, in the one human brain examined in the present experiments, the mean Li concentrations varied from 0.09 to 1.49 meq/kg, (factor of 15). There might be therefore a much greater variability in Li values for the human brain.

When examined in Table 2, it could be seen that the 9 monkey brain areas with the highest Li levels differed statistically from all the others ($p<0.05$). The extremely high urine Li concentrations (13.7 meq/l), after a 3 6 week period of oral Li intake, indicated that the urinary tract was

TABLE 4

BRAIN AND OTHER ORGANS OF A MANIC DEPRESSIVE PATIENT WHO DIED OF EXCESS ALCOHOL AND DARVON INGESTED BUT WITH A THERAPEUTIC LITHIUM BLOOD LEVEL

Brain part	Li-meq/kg	Other organs	Li-meq/kg
Retrosplenial Cingulate Gyrus	1.49	Whole blood*	0.86
Caudate Nucleus	1.21	Bile*	7.8
Hypothalamus, anterior	0.89	Bone	2.5
Hippocampus	0.76	Cardiac muscle	1.4
Cortex, occipital	0.75	Lymphoid tissue	1.3
Thalamus, anterior nuclei	0.65	Thyroid	1.1
Globus pallidus	0.56	Pituitary	0.9
Substantia nigra	0.56	Kidney (whole)	0.9
Cortex, frontal (frontal Pole)	0.45	Lung	0.8
Corpus callosum	0.44	Fat	0.7
Hypothalamus, posterior	0.36	Spleen	0.7
Hippocampus, fimbria	0.36	Alveolar connective tissue	0.6
Amygdala	0.36	Liver	0.4
Thalamus, posterior nuclei	0.32	Testis	0.3
Cortex, temporal lobe	0.19	Femoral Nerve	0.2
Subcallosal Cingulate gyrus	0.19		

Male, age 36. Autopsy 12 hr after death. Organs frozen and flown to Pittsburgh. Li dosage: 1200 mg daily for 3 months after final acute episode.

*Whole blood and bile Li values are expressed in meq Li/L.

the most important excretory organ (Table 3). There was, however, a Li concentration in the feces of 3.3 meq/kg which indicated that a considerable amount of Li was either not absorbed at all or went into the bile and eventually back into the GI tract for excretion (Table 3). This was not true for the human where little or no Li was found in the feces after oral Li therapy according to Schou, *et al.* [6]. No sample of feces from my patient was sent for examination. The concentration of Li in the bile of the monkeys reached a level of 3.80 meq/l. Both in man and more so in the monkeys, the ratio of Li in the thyroid to that in blood was somewhat greater than 1, indicating the possibility of some active transport of Li against a concentration gradient in this organ. This is of interest since a mild degree of hypothyroidism did develop in a number of patients under Li therapy [7] and this state apparently reverted to normal after Li therapy was terminated or was correctable by the concomitant use of small doses of thyroxine [7]. Other monkey organs which appeared to concentrate Li against a gradient were nails (13.6 meq ± 9.80) and bone (1.72 meq/kg ± 0.38 or 1.72 ± 0.52). In the present study the submaxillary gland of monkeys reached a Li concentration of 1.17 meq/kg ± 0.25, a level slightly higher than in the serum. The same is true for some areas of skin and the lens of the eye of these animals. Hair itself attained a concentration of only 0.6 ± 0.1 meq/kg. Forty-four other monkey organs which were examined had Li concentrations varying from 0.25 ± 0.05 meq/kg to 1.0. For man, 2 brain areas (retrosplenial cingulate gyrus and the caudate nucleus) actually attained considerably higher values than those of whole blood whereas there were no such values for brain areas in the case of the monkeys.

Previously Spring and Spirtes [8] had demonstrated that active transport of Li occurred in the submaxillary gland in the cat. Further exidence for active transport of Li in mammals had been presented by Post [5] who showed that Li^+ could substitute for K^+ in the active transport of the latter across the membrane of the human erythrocyte. Likewise, it is known that Li enters the erythrocyte mainly by diffusion at the same rate as Na^+ but is actively extruded at 1/20 the rate [2]. This could also lead to an accumulation of Li intracellularly and to a ratio of Li concentration/Li extracellular of more than one as indicated in the present experiments for some monkey organs and two human brain regions. However, it is not believed that the organs showing Li ratios (organ Li concentration/serum Li concentration) of slightly over 1 in this study can be considered as supportive for the idea of active transport of Li in these areas.

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