At this time it is impossible to differentiate the mechanism of drug action with the limited data at hand. There are two apparent areas for further investigation. The first deals with the effect of methylphenidate on fixation reactions of CO_2 involved in cholesterol formation. The second possibility, the differential incorporation of methyl- and carboxyl-labeled acetate into the sterol nucleus, suggests some change in the tricarboxylic acid cycle. Further work is necessary before the mechanism of methylphenidate on brain cholesterol can be elucidated.

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Fate of intravenously injected iodate and periodate

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BECAUSE its relation with thyroid physiology iodide metabolism has been thoroughly studied but little[1–3] is known about the distribution and elimination of iodate and periodate after intravenous administration.

The ^{131}I-iodate has been prepared by oxidation of ^{131}I-iodine with an excess of sodium chlorate[4] and the ^{131}I-metaperiodate by oxidation of the ^{131}I-iodate with chlorine in alkaline solution.[5] The radiochemical purity of these labelled compounds was assayed chromatographically. 20 μc of ^{131}-I-labelled iodate (specific activity 5 μc/mg, or 10 μc of ^{131}I-labeled potassium metaperiodate (specific activity 10 μc/mg) dissolved in 0·1 ml of distilled water, were injected into adult Wistar rats through the tail vein. Groups of 5 animals (three males and two females) were sacrificed at different intervals and the activity in organs and tissues was determined with a scintillation counter. After this, the organs were homogenized 0·01 N in sodium hydroxide and the supernatant sample analyzed by ascending chromatography on paper Whatman 3 MM and using *n*-propanol: water: 15 N ammonium hydroxide (30 : 10 : 5). With this solvent the R_f values are: Iodate 0·14–0·20, metaperiodate 0·00–0·02 and iodide 0·56–0·62.

The examination of the specific activity (count/min per g tissue) found in the various organs after the injection of ^{131}I-labelled iodate (Table 1) shows a maximum during the first hour, with exception of the stomach, which has a maximum at 6 hr. This peak of stomach activity is accompanied by an increase in kidney, intestine, parotid gland, muscle and bone. In the ^{131}I-labelled metaperiodate (Table 2) the maximum of specific activity was found at 6 hr after the injection and only the intestine presented its highest value before (3 hr).

The chromatographic analysis performed on the different tissues (Table 3) indicates that a considerable amount of radioactivity has been found in the liver as iodate.

The whole body counting (Fig. 1) shows a similar pattern of elimination for both iodate and metaperiodate. Fifty per cent of the injected radioactivity is eliminated under these experimental conditions, at 7 hr for the iodate and at 18 hr for the metaperiodate. All the values given in Tables 1 and 2 as well as in Fig. 1 have been corrected for the radioactive decay.

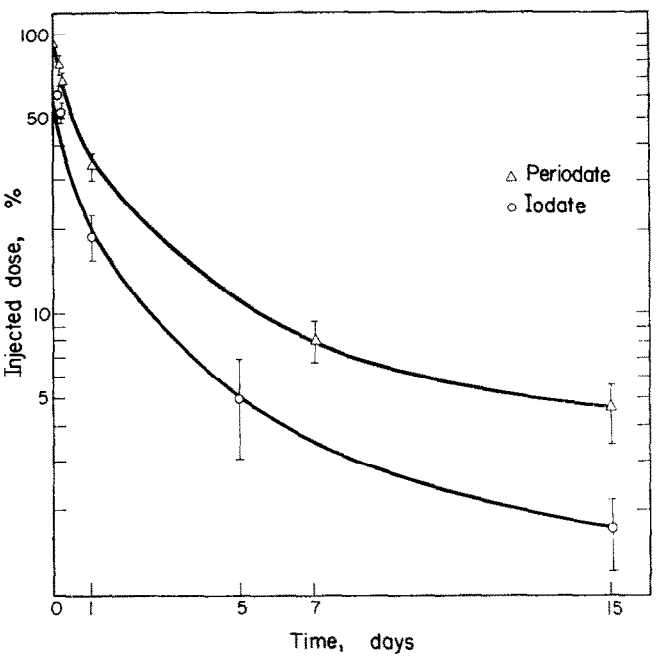

FIG. 1

DISCUSSION

Immediately after the iodate injection it is distributed throughout the whole body. Later, the liver concentrates the iodate because after 24 hr no iodate was found in stomach and intestine, only 4 per cent appeared in kidney and 98 per cent in liver. According to all these observations the reduction of iodate to iodide occurs in the liver which later eliminates the iodide through the gastric mucose.

On the other hand the metaperiodate seems to be reduced to iodate as soon as it is injected and is metabolized as iodate. The correspondence between the maximum activity observed in the stomach and the increase in kidney, parotid gland, muscle and bone could be explained as a temporary increase in the blood activity by a reabsorption of the radioiodide through the intestine. The fact that iodate has not been found in intestine while it was present in the stomach (Table 3 periodate values at 1 hr) could be due to the stomach pH which assures its reduction to iodine according to the following redox reaction:

$$10_3^- + 6H^+ + 5e \rightleftharpoons 1/2\, I_2 + 3\, H_2O$$

TABLE 1. VALUES OF THE RADIOACTIVITY FOUND IN THE DIFFERENT TISSUES AFTER THE INJECTION OF RADIOIODATE

		1 hr	3 hr	6 hr	1 day	5 days	15 days
Bone	a	1555 ± 265c	512 ± 138	644 ± 66	139 ± 12	31 16	27 8
Brain	a	202 ± 86	60 ± 19	57 ± 12	94 ± 7	9 ± 3	1 ± 0·2
	b	0·13 ± 0·07	0·03 ± 0·01	0·03 ± 0·01	0·06 ± 0·03	0·008 ± 0·003	0·001 ± 0·001
Carcass*	b	46·50 ± 8·16	11·82 ± 3·25	10·10 ± 4·86	11·05 ± 5·60	4·25 ± 1·86	0·93 ± 0·31
Excreta†	b	9·05	37·65	45·96	76·45	93·36	98·21
Heart	a	155 ± 346	733 ± 225	669 ± 128	136 ± 36	15 ± 8	6 ± 2
	b	0·48 ± 0·12	0·22 ± 0·10	0·19 ± 0·09	0·05 ± 0·02	0·006 ± 0·002	0·002 ± 0·001
Intestine	a	975 ± 125	441 ± 160	605 ± 80	45 ± 16	36 ± 18	31 ± 12
	b	6·08 ± 2·30	2·20 ± 1·25	2·68 ± 1·01	2·91 ± 0·56	0·19 ± 0·06	0·003 ± 0·001
Kidney	a	2070 ± 465	806 ± 220	851 ± 265	128 ± 36	20 ± 3	15 ± 2
	b	1·56 ± 0·45	0·62 ± 0·24	0·59 ± 0·19	0·11 ± 0·02	0·02 ± 0·002	0·002 ± 0·001
Liver	a	1216 ± 320	734 ± 320	578 ± 286	113 ± 36	44 ± 18	4 ± 2
	b	5·55 ± 1·02	2·99 ± 0·86	2·13 ± 0·50	0·49 ± 0·16	0·19 ± 0·08	0·002 ± 0·001
Lung	a	2319 ± 664	1442 ± 362	821 ± 164	151 ± 80	15 ± 8	11 ± 6
	b	1·67 ± 0·62	0·74 ± 0·18	0·46 ± 0·06	0·17 ± 0·08	0·01 ± 0·008	0·001 ± 0·001
Muscle	a	424 ± 195	175 ± 63	219 ± 36	44 ± 18	8 ± 2	4 ± 1
Ovary	a	1150 ± 365	623 ± 146	376 ± 58	108 ± 20	12 ± 6	4 ± 2
	b	0·22 ± 0·10	0·11 ± 0·04	0·05 ± 0·02	0·03 ± 0·01	0·002 ± 0·001	0·002 ± 0·001
Parotid	a	1392 ± 254	528 ± 226	574 ± 205	95 ± 43	11 ± 6	4 ± 1
Gland	b	0·36 ± 0·19	0·12 ± 0·10	0·15 ± 0·06	0·02 ± 0·006	0·003 ± 0·001	0·002 ± 0·001
Spleen	a	1182 ± 228	670 ± 165	503 ± 187	99 ± 60	15 ± 9	3 ± 2
	b	0·42 ± 0·12	0·25 ± 0·09	0·17 ± 0·10	0·04 ± 0·02	0·006 ± 0·003	0·002 ± 0·001
Stomach	a	11788 ± 1022	23121 ± 865	25110 ± 2046	3492 ± 289	67 ± 32	52 ± 36
	b	24·10 ± 5·96	41·83 ± 13·61	37·12 ± 8·20	4·13 ± 1·60	0·20 ± 0·06	0·001 ± 0·001
Testis	a	958 ± 276	496 ± 90	757 ± 62	100 ± 36	13 ± 1	4 ± 1
	b	0·68 ± 0·21	0·24 ± 0·08	0·53 ± 0·15	0·05 ± 0·01	0·01 ± 0·006	0·003 ± 0·001
Thyroid	a	36890 ± 2965	41750 ± 8036	25380 ± 2025	12130 ± 3065	33760 ± 2642	61900 ± 5874
	b	0·24 ± 0·08	0·27 ± 0·16	0·16 ± 0·09	0·08 ± 0·01	0·33 ± 0·09	0·55 ± 0·06

* = Skin + skeleton + muscles. † = Urine + Faeces (cumulative values).
a = Specific Activity (per g). b = Per cent of injected dose. c = Standard deviation.

TABLE 2. VALUES OF THE RADIOACTIVITY FOUND IN THE DIFFERENT TISSUES AFTER THE INJECTION OF RADIOPERIODATE

		1 hr	3 hr	6 hr	1 day	7 days	15 days
Bone	a	263 ± 46*c*	557 ± 34	591 ± 166	251 ± 72	32 ± 8	7 ± 2
Brain	a	28 ± 3	51 ± 15	146 ± 16	48 ± 6	3 ± 1	1 ± 1
	b	0·02 ± 0·003	0·03 ± 0·01	0·10 ± 0·01	0·04 ± 0·006	0·001 ± 0·0003	0·005 ± 0·0009
Carcass*	b	80·90 ± 13·45	62·15 ± 15·40	48·96 ± 12·23	19·34 ± 8·75	1·22 ± 0·98	0·25 ± 0·10
Excreta†	b	7·65	20·68	33·56	66·56	91·40	93·60
Heart	a	308 ± 121	510 ± 208	854 ± 126	304 ± 69	8 ± 2	—
	b	0·15 ± 0·09	0·24 ± 0·10	0·35 ± 0·09	0·18 ± 0·03	0·006 ± 0·001	—
Intestine	a	348 ± 72	703 ± 265	661 ± 286	452 ± 203	50 ± 46	2 ± 1
	b	3·21 ± 1·32	5·16 ± 2·15	4·33 ± 1·64	2·81 ± 1·23	0·78 ± 0·34	0·05 ± 0·02
Kidney	a	351 ± 120	537 ± 201	633 ± 126	266 ± 102	17 ± 3	4 ± 4
	b	0·44 ± 0·13	0·56 ± 0·20	0·68 ± 0·13	0·30 ± 0·09	0·03 ± 0·003	0·01 ± 0·007
Liver	a	251 ± 96	437 ± 163	678 ± 196	270 ± 136	12 ± 11	910 ± 164
	b	1·67 ± 0·71	2·42 ± 0·46	3·64 ± 1·12	1·69 ± 0·48	0·14 ± 0·08	1·69 ± 0·54
Lung	a	247 ± 106	369 ± 216	945 ± 473	304 ± 96	15 ± 4	2 ± 1
	b	0·27 ± 0·10	0·37 ± 0·22	0·85 ± 0·31	0·34 ± 0·09	0·02 ± 0·002	0·006 ± 0·006
Muscle	a	62 ± 46	160 ± 58	209 ± 86	103 ± 35	103 ± 35	4 ± 1
Ovary	a	378 ± 106	1014 ± 224	966 ± 167	492 ± 94	18 ± 4	1 ± 1
	b	0·07 ± 0·03	0·20 ± 0·09	0·18 ± 0·08	0·13 ± 0·06	0·01 ± 0·006	0·003 ± 0·001
Parotid	a	262 ± 65	512 ± 266	816 ± 89	283 ± 73	—	14 ± 3
Gland	b	0·10 ± 0·02	0·24 ± 0·10	0·24 ± 0·09	0·09 ± 0·002	—	0·02 ± 0·005
Spleen	a	287 ± 124	672 ± 262	1143 ± 349	367 ± 153	13 ± 4	6 ± 3
	b	0·12 ± 0·06	0·23 ± 0·08	0·35 ± 0·19	0·13 ± 0·05	0·008 ± 0·002	0·006 ± 0·001
Stomach	a	1761 ± 406	5121 ± 2726	8147 ± 3946	6920 ± 2051	18 ± 3	5 ± 2
	b	2·72 ± 0·75	5·66 ± 2·06	6·32 ± 3·18	6·49 ± 2·46	0·09 ± 0·01	0·03 ± 0·01
Testis	a	87 ± 16	217 ± 112	388 ± 69	146 ± 29	11 ± 2	4 ± 1
	b	0·11 ± 0·04	0·28 ± 0·09	0·41 ± 0·22	0·21 ± 0·06	0·004 ± 0·001	0·005 ± 0·0001
Thyroid	a	48540 ± 6856	80990 ± 26724	42920 ± 8324	186540 ± 25622	319073 ± 71324	92074 ± 6721
	b	0·53 ± 0·08	0·89 ± 0·16	0·53 ± 0·10	2·29 ± 0·51	6·44 ± 0·96	3·72 ± 0·72

* = Skin + skeleton + muscles. † = Urine + Faeces (cumulative values).
a = Specific Activity (cpm/g). b = Per cent of injected dose. c = Standard deviation.

TABLE 3. CHROMATOGRAPHIC ANALYSIS—VALUES OF THE FOUND ACTIVITY IN THE HOMOGENIZED ORGANS*

	Supernatant As Radioiodide (%)	Supernatant As Radioiodate (%)	(activity remaining in pellet (%)
After iodate injection	94·8	3·9	1·2
Liver	1·9	92·1	6·0
Stomach	96·8	—	3·2
Intestine	94·9	—	5·1
Urine	87·7	12·3	—
Feces	99·0	—	1·0
After periodate injection			
Kidney	4·0†	94·2†	1·8†
	97·0	1·9	1·0
Liver	18·1†	72·6†	9·3†
	7·5	88·2	4·3
Stomach	76·3†	19·0†	4·6†
	97·7	—	2·3
Intestine	96·1†	—	3·9
Intestine	95·7	—	4·3
Urine	100·0	—	—
Feces	99·0	—	1·0

* As a percentage of the total activity

† = Values 1 hr after the injection, the other values correspond to 1 day after the injection.

In our experiment the intestine which according to Postan[2] excretes the iodide does not eliminate the iodate. Also, a part of the radioactivity is excreted through the urine in both chemical forms, as iodide and as iodate but through the feces only as iodide.

The delay observed in the elimination of metaperiodate may be related with general inflammation in the vicinity of the site of injection. For a correct evaluation of the radioactivity balance Regoeczi's observation[6] that approximately 25 per cent of the animal's iodide pool is localized in the skin must be considered.

The importance of the liver in the deiodination of ^{131}I-labeled organic molecules has been previously studied by Chaikoff,[7] Straub[8] and the author[9, 10] but, in this case the de-iodination occurred by splitting off the radioiodine.

SUMMARY

The distribution in various organs and tissues of the rat at different times of intravenously injected ^{131}I-labelled iodate and metaperiodate has been studied.

This study showed that the liver concentrates and reduces the iodate to iodide which is eliminated through the gastro-intestinal tract. In the first day half of the injected radioactivity was excreted. The chromatographic analysis of the excretas showed that in urine both iodide and iodate were present but in feces only iodide.

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