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Fluoride Tissue Distribution: Intracellular Fluoride Concentrations (40904)[1]

W. D. ARMSTRONG AND LEON SINGER

Department of Biochemistry, Medical School, University of Minnesota, Minneapolis, Minnesota 55455

Abstract. The distribution of fluoride and chloride in muscle, liver, and tendon was studied in groups of 6–15 rats sacrificed at 80–240 min after intraperitoneal injections containing radiofluoride (^{18}F) and radiochloride (^{36}Cl). Liver exhibited a constant ^{18}F(tissue water):^{18}F(plasma water) ratio over 120–220 min and this ratio was constant in muscle over 80–120 min. The $^{18}F_{tw}/^{18}F_{pw}$ ratios for muscle were lower than those of liver. The ratios of ^{18}F distribution for both liver and muscle declined significantly at the longest time periods probably as a result of reductions of intracellular pH and/or increases of extracellular pH. Chloride space volumes were determined from chloride analyses of the tissues and plasma and confirmed by the ^{36}Cl(tissue water):^{36}Cl(plasma water) ratios. The fluid space volumes and the ^{18}F(tissue water):^{18}F(plasma water) ratios were used to indicate that the average intracellular ionic fluoride concentrations of liver and muscle are, respectively, 79 and 38% that of plasma water. The relative intracellular fluoride concentrations of liver and muscle are related to their respective values of intracellular pH. The entire water of tendon was found to be available to chloride, analytically determined, and to ^{36}Cl and ^{18}F.

Fluoride is a constituent of mammalian tissues and there is evidence of penetration of this ion into intracellular fluids. *In vitro* experiments using radioactive (^{18}F), in which cells could be separated from plasma or culture media, demonstrated the labeled ion in cell waters. Thus, it was shown by us (1) that ^{18}F added to blood at pH 7.4 quickly reached a concentration in red-cell water which was 66% of that of plasma water. Similarly, Drescher and Suttie (2) found the ^{18}F contents of cell waters of mouse fibroblasts and of HeLa cells to be about 37% that of the culture media when ^{18}F was added to the media.

We reported (3) ratios of distribution of ^{18}F between the waters of seven soft tissues and plasma of a few rats 80 min after injection of ^{18}F. These ratios, except for tendon, were less than 1.0 but greater than the tissue water of plasma water ratios of chloride in muscle, liver, skin, heart, and testes. These findings suggested intracellular penetration of ^{18}F *in vivo*. Recently, Whitford, Pashley, and Reynolds (4) presented results of determination of ratios of distribution of ^{18}F between tissue waters of 12 soft tissues and plasma (T/P ratios) of rats at intervals of 5 to 60 min after intravenous injections of ^{18}F in the carrier free state and when injected with carrier fluoride. Several of the tissue waters, including that of liver, reached a steady-state distribution of ^{18}F with plasma within 60 min, as indicated by constant T/P ratios over time, but skeletal muscle, for example, did not.

In our earlier study (3) and in that of Whitford, Pashley, and Reynolds (4) no allocation was made of ^{18}F present in intracellular fluids of the tissues. We now report the results of *in vivo* attained relative ^{18}F concentrations of extracellular and intracellular fluids of liver and muscle of rats over periods of 80 to 240 min after injection of ^{18}F. Tail tendon was also examined because, unlike many other tissues, there is evidence (5) that chloride is distributed through the entire tendon water and because of its high fluoride content.

The estimates of volumes of intracellular fluids containing fluoride were obtained from the excess volumes of distribution of ^{18}F in tissue fluids over the volumes of chloride space, the latter being obtained from chemical analyses for chloride in plasma and tissues and confirmed by the distribution of radiochloride (^{36}Cl) between tissue and plasma waters. Chloride space was taken to be equivalent to extracellular

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space for which there is supporting evidence for liver (6) and for muscle (7). Implicit in the calculation of intracellular ^{18}F contents is the assumption that there is no significant binding of ^{18}F to tissue components.

The two radioisotopes (^{18}F and ^{36}Cl) were injected in the same solution. The time after injection at which ^{36}Cl reached complete distribution through the chemically determined tissue chloride (constant chloride specific activity) was taken as an indication that sufficient time has lapsed for the halogen ions in the injectates to have been completely absorbed and this also furnished one boundary of time needed for ^{18}F to be distributed through the fluids of the tissues examined.

Materials and methods. Male rats (Sprague–Dawley strain) were fed Purina Lab Chow (ca 40 ppm fluoride) and tap water (1.0 ppm fluoride) until their body weights attained 200 ± 5 g. Food was removed from the cages 24 hr prior to each experiment. Groups of six to eight animals were injected intraperitoneally at recorded times with 1.5 ml saline solution containing radiofluoride (^{18}F) and/or radiochloride (^{36}Cl). The radiofluoride was carrier free. The animals were lightly anesthetized with ether and sacrificed by exsanguination by heart puncture at one of the following time periods: 80, 120, 160, 200, 240 min and 17 hr after the injection given each animal. Duplicate experiments with some tissues were carried out on different occasions with groups of animals at 80 and 220 min.

Plasma from heparinized blood was separated and samples of thigh, shoulder, and leg muscle, liver, and tail tendon were rapidly removed. Liver and muscle samples were blotted and quickly wrapped in weighted Parafilm, to reduce water loss by evaporation, and weighed. Special care was taken quickly to enclose the tendon samples within Parafilm immediately after their removal from the tails. Other animals, entirely comparable to those mentioned, were sacrificed and plasma and tissues obtained as described for additional determinations of their chloride and water contents. Water was determined by loss on drying at 105°C. Fat-free contents were obtained by extracting the dried tissues with a 50:50 absolute ethyl alcohol–ethyl ether mixture.

Well-type crystal scintillation counters were used for ^{18}F counting by detection of the annihilation gamma radiation from absorption of the positrons produced by decay of this radionuclide. With well-type crystal detectors the count rate observed with a sample is affected slightly but significantly by its volume, i.e., height in the counting tube. Therefore, to maintain uniform "geometry" of samples with respect to the photon crystal detector, 2 ml of plasma samples were used and minced samples of liver and muscle were packed to equal heights in the plastic counting tubes. Since the volumes of tail tendons were small, weighted samples were dissolved by heating in 3 ml 5 *N* NaOH in the counting tubes. Appropriate dilutions of the injection solutions served as standards and were counted in 1.0-, 2.0-, and 3.0-ml volumes with a selection between these being made according to the height of the sample in each counting tube.

The ^{18}F counts were made over 2, 4, 6, or 8 min as needed to obtain approximately 10,000 counts (not obtained with tendon samples at 240 min) and the clock time of the start of each sample count was recorded. In addition to the normal background count, the ^{18}F counts were corrected for the effect of photons arising from ^{36}Cl as a consequence of positron emission and electron capture, minor modes of decay of ^{36}Cl. This was done by recounting all samples and standards with crystal scintillation counters after 2–3 days when the ^{18}F had decayed. This correction was small, but real, and amounted to about 20–30% of the normal background count. All ^{18}F net counts in each experiment were adjusted for decay over the time period from a zero time to the mid-point to the clock time of each sample count by use of the decay constant derived from the 109.7-min half-life of ^{18}F (8).

End-window β counters were used for ^{36}Cl counting a few days after the ^{18}F counts were made. One-inch-diameter steel dishes with vertical walls were used. One-milliliter volumes of plasma and of solutions of tendon in 5 *N* NaOH were counted. Liver and

muscle were dried and ground to fine powders and 400-mg aliquots were packed into counting dishes. The standards were 1.0 ml of a dilution of the injection solution or, for liver and muscle, 400 mg of NaCl which had been mixed with a known volume of the injection solution and dried. No corrections for decay of ^{36}Cl were required because of its long half-life.

Chloride was determined by the method of Castor, McDonald, and Armstrong (9) or by use of the Buchler–Cotlove Chloridometer. The total fluoride content of tendon was determined in separate experiments by our microdistillation method (10).

Mean results and standard errors of the means are given in the tables; the values of n are shown in parentheses. Comparisons of group means for significant differences were made by Student's t test.

Results. Table I gives the directly determined results of analyses of plasma and tissues for water and chloride; the water contents on a fat-free, fresh basis are given in Table III. Table II presents the results of distribution of the halogen ions between tissue and plasma waters. The ratios of chemically determined chloride (^{35}Cl) are those of meq chloride/kg tissue water (tw) to meq chloride/kg plasma water (pw). The ratios of ^{36}Cl and ^{18}F were obtained by dividing the percentage of an injected radioisotope in a volume of tissue water by that in an equal volume of plasma water. All ratios, with one exception, were obtained from the results of water determinations, chloride analyses, and assays for ^{18}F and ^{36}Cl in the tissues and plasma of individual animals. The exception was that 117.5 meq ± 1.51 (n = 20) chloride/kg tendon water was used to calculate $^{35}Cl_{tw}/^{35}Cl_{pw}$ ratios of tendons since these tissue samples were insufficient in amount to permit analyses for chloride and $^{18}F-^{36}Cl$ assays. The mean chloride content of tendon water was obtained from animals sacrificed for this purpose.

The results shown as $^{35}Cl_{tw}/^{35}Cl_{pw}$ and $^{36}Cl_{tw}/^{36}Cl_{pw}$ could have been given as specific activities. When expressed as ratios of specific activities of chloride in tissue and plasma waters all results, except for tendon at 80 min, were close to 1.0. However, since the results for ^{18}F distribution were available only as $^{18}F_{tw}/^{18}F_{pw}$ ratios, the results for chloride distribution are shown in the same manner in Table II.

The total fluoride (i.e., ionic plus bound fluoride) content of tail tendon was 0.66 ± 0.053 ppm. Excluding calcified tissues and pathological calcifications, tendon appears to have the highest tissue fluoride content reliably reported. Tendons were removed from muscle samples but they undoubtedly retained some fibrous tissue as fasciae and septae.

Discussion. The results support those previous findings (5) which indicated that the entire water of tendon is available to chloride. This was demonstrated (Table II) by the ratios of both ^{35}Cl and ^{36}Cl in tendon and plasma waters being in agreement[2] and close to 1.0 after 80 min. However, 80 min after the injections did not suffice for ^{36}Cl (see footnote to Table II) to equilibrate between tendon and plasma waters. ^{18}F of tendon water likewise had a concentration only 80% that of plasma water at 80 min. Evidently there was an impedance in delivery of both labeled ions to tendon fluids, presumably caused by circulatory or diffusion factors. By 120 min ^{18}F, like chloride, had become uniformly distributed through tendon and plasma waters (P, tendon $^{18}F_{tw}/^{18}F_{pw}$ 120 min vs 160 min, not significantly different). The ratios of $^{18}F_{tw}/^{18}F_{pw}$ for tendon over the interval 120–200 min, being close to 1.0, are in contrast to a similar ratio of 1.86 previously reported by us (3). Some loss of water occurred in dissection and handling of the tail tendon samples in the earlier study but this does not account completely for the high $^{18}F_{tw}/^{18}F_{pw}$ found.

It appears that the techniques used in the present study effectively prevented loss of water from the tendon samples since the ratio of chloride in tendon water to that in plasma was very nearly 1.0 (Table II).

Tendon $^{18}F_{tw}/^{18}F_{pw}$ ratios were also derived from the results at 240 min; the mean

[2] The results of distribution of ^{35}Cl and ^{36}Cl in tendon and plasma when converted to specific activities yielded 0.99 ± 0.007(32) for the ratio of specific activity of tendon tissue water to that of plasma water.

TABLE I. COMPOSITION OF PLASMA AND TISSUES

	Plasma	Liver	Muscle	Tendon
Water g/kg, fresh	933 ± 1.40 (38)	703 ± 1.3 (59)	752 ± 1.4 (59)	631 ± 1.95 (41)
Chloride meq/kg, fresh	107.8 ± 0.57 (38)	32.0 ± 0.43 (26)	13.1 ± 0.28 (39)	74.1 ± 1.24 (20)
meq/kg, fat-free, fresh		33.6 ± 0.45 (26)	13.4 ± 0.28 (39)	75.0 ± 1.26 (20)
meq/kg, tissue water	115.5 ± 0.61 (38)	45.7 ± 0.58 (26)	17.4 ± 0.39 (39)	117.5 ± 1.51 (20)

result was 1.9 ± 0.47 (n = 6). The large variation among the individual results was caused by the comparatively poor ^{18}F counting statistics as a consequence of the low amount of ^{18}F remaining undecayed at 240 min after the injections in the small tendon samples. This high mean value of $^{18}F_{tw}/^{18}F_{pw}$ at 240 min was not due to loss of water from the tendon samples during dissection because the $^{36}Cl_{tw}/^{36}Cl_{pw}$ ratio of the same samples was 0.98 ± 0.016, n = 6. This finding with respect to fluoride, to the extent it is reliable, implies that by 240 min some ^{18}F had become incorporated into tendon constituents perhaps by exchange for bound fluoride.

Our results for distribution of ^{18}F between liver and muscle waters and plasma at 80 min and at later times are lower than those found by Whitford, Pashley, and Reynolds (4) at 60 min but a large part of this difference in results is due to the fact that the earlier workers reported ratios of ^{18}F in tissue water to that in plasma whereas we divided ^{18}F in tissue water by that in plasma water.

We found the water of muscle to be in kinetic equilibrium with respect to ^{18}F by 80 min, as indicated by equal $^{18}F_{tw}/^{18}F_{pw}$ values, at 80 and 120 min. As pointed out in the introduction Whitford et al (4) found resting abdominal wall muscle not to be kinetically homogeneous with plasma with respect to ^{18}F distribution at 60 min. Their animals were anesthetized and immobile over the period from the injection of ^{18}F until they were sacrificed while those used in the current study were awake and probably as ac-

TABLE II. DISTRIBUTION OF CHLORIDE (^{35}Cl AND ^{36}Cl) AND RADIOACTIVE FLUORIDE (^{18}F) BETWEEN TISSUE AND PLASMA WATERS

	Liver	Muscle	Tendon
$^{35}Cl_{tw}/^{35}Cl_{pw}$	0.39 ± 0.007 (26)	0.15 ± 0.003 (39)	1.01 ± 0.005 (20)
$^{35}Cl_{tw}/^{36}Cl_{pw}$	0.39 ± 0.005 (39)	0.16 ± 0.002 (46)	1.01 ± 0.007 (30)[a]
$^{18}F_{tw}/^{18}F_{pw}$[b]			
80 min	0.82 ± 0.024 (7)	0.51 ± 0.019 (15)	0.80 ± 0.036 (16)
		[0.49 ± 0.026 (7);	[0.71 ± 0.059 (7);
		0.53 ± 0.028 (7)]	0.88 ± 0.028 (9)]
120 min	0.91 ± 0.014 (8)	0.54 ± 0.035 (8)	0.93 ± 0.036 (8)
160 min	0.92 ± 0.017 (8)	—	0.97 ± 0.062 (7)
200 min	—	—	1.02 ± 0.024 (8)
220 min	0.89 ± 0.038 (13)	0.40 ± 0.012 (14)	—
	[0.79 ± 0.014 (6);	[0.38 ± 0.012 (7);	
	0.97 ± 0.052 (7)]	0.42 ± 0.010 (7)]	
240 min	0.76 ± 0.062 (6)	0.41 ± 0.06 (6)	—

[a] Values of $^{36}Cl_{tw}/^{36}Cl_{pw}$ with a mean of 0.92 ± 0.025 (n = 16) for tendon at 80 min not included (see text) but includes values of this ratio at 17 hr with a mean of 1.02 ± 0.011 (n = 9). All other results of this ratio for tendon for liver and muscle combined since no significant variations were obtained for ^{36}Cl distribution over 120 min–17 hr for tendon or over 80 min–17 hr for liver and muscle. All $^{35}Cl_{tw}/^{35}Cl_{pw}$ ratios for each tissue combined.

[b] Some values of $^{18}F_{tw}/^{18}F_{pw}$ are the combined results of two studies carried out several weeks apart. The results of each of the two replicate studies are given in the square brackets.

TABLE III. FLUID SPACE VOLUMES AND INTRACELLULAR FLUID FLUROIDE CONCENTRATIONS

	Liver	Muscle	Tendon
1. Total water (tw) (ml/kg FFF wt)[a]	738 ± 1.4 (59)	770 ± 1.4 (59)	639 ± 2.0 (41)
2. Chloride space (ECF) (ml/kg FFF wt)[b]	274 ± 4.6 (26)	111 ± 2.6 (40)	[c]
3. Intracellular space (ICF) (ml/kg FFF wt): 1–2	464 ± 4.8 (26)	659 ± 2.9 (40)	
4. Intracellular fluoride conc. (%$[F^-]_{pw}$)			
80 min	[d]	43	
120 min	85	46	
160 min	87		
220	82	30	
240	62	31	
Average	79	38	

[a] FFT wt is fat-free fresh weight.
[b] Chloride space (ml) = meq chloride (^{35}Cl) per kg FFF wt × 0.96 × 1000/meq chloride (^{35}Cl)/kg plasma water, where 0.96 is the Donnan factor for chloride (1,18).
[c] Chloride space of tendon coextensive with total water space (see text).
[d] Value omitted from average since $^{18}F_{tw}$ of liver not in equilibrium with $^{18}F_{pw}$ at 80 min (see text).

tive as normal rats. This would tend to increase muscle blood flow by opening capillaries.

However, in contrast to muscle, an equilibrium of distribution of ^{18}F not established in liver at 80 min (P:80 min vs 120 min < 0.005). This delay with liver was not, however, exhibited by ^{36}Cl since the $^{36}Cl_{tw}/^{36}Cl_{pw}$ ratio at 80 min was 0.41 ± 0.005, n = 16, which is quite like the overall ratio of $^{36}Cl/^{36}Cl$ of 0.39 ± 0.005, n = 39. Liver did exhibit constant $^{18}F_{tw}/^{18}F_{pw}$ ratios between 120 and 220 min.

An unexpected observation is the apparent reduction in relative ^{18}F concentration in some tissue waters to that of plasma water in liver and muscle at the longer time periods after administration of ^{18}F (Table II). Thus, liver $^{18}F_{tw}/^{18}F_{pw}$ ratio at 240 min (0.76) is lower than 0.92 at 160 min (P < 0.01) and the lower of the two values for liver at 220 min (0.79) is distinctly depressed from 0.91 at 120 min and 0.92 at 160 min (P < 0.01). In muscle the $^{18}F_{tw}/^{18}F_{pw}$ ratios of 0.40 at 220 min and 0.41 at 240 min are both lower than 0.54 at 120 min (P < 0.0005 and 0.05, respectively). Possible explanations of these findings are: (a) incorporation of ^{18}F by exchange for ^{19}F (stable fluorine) in nonionic forms in liver and muscle at the early time periods when the ^{18}F concentration of plasma was elevated (4) with a reverse exchange at later times when fluoride specific activity of extracellular fluids are markedly reduced, (b) formation at the later time periods of nondiffusible states of combination of ^{18}F and the occurrence of these forms of bound fluoride, labeled with ^{18}F, in plasma, and (c) a decrease of intracellular pH (pH_i) or an increase of pH of plasma, both of which would cause a redistribution of ^{18}F from cellular waters into plasma water. This is a known effect of the indicated changes of pH since hydrogen fluoride (HF) is the form which traverses cell membranes (4, 11, 12).

The effect of changes of pH_i on distribution of ^{18}F between tissue and plasma waters of muscle and liver can be calculated by use of an equation (13, 14) developed to calculate pH_i from 5,5-dimethyl-2,4-oxazolidinedione (DMO) distribution in tissue and plasma waters, first employed by Whitford, Pashley, and Reynolds (4) in fluoride studies. In its present application the equation employs $^{18}F_{tw}/^{18}F_{pw}$ ratios, the ratios of extracellular to intracellular fluid volumes (Table III) and an assumed plasma pH of 7.40. Thus, the pH_i of muscle at 80–120 min was 7.04 and at 220–240 min it was 6.87. Liver pH_i, using the average values of $^{18}F_{tw}/^{18}F_{pw}$ ratios at 120, 160, and 220 min, was 7.32 and had declined to 7.19 at 240 min.

Excluding the remote possibilities of binding of ^{18}F to tissue components at the early time periods and to plasma constitutients at the later periods, the values of pH_i given are valid comparative estimates of intracellular pH of liver and of muscle when the plasma pH is constant at 7.40.

Since the factor $10(pH_e - pK_a)$, where pH_e is plasma pH and pK_a is 3.45 (i.e., the pK_a of HF) is used as a multiplier in the equation (13, 14) for calculation of intracellular pH, increments of plasma pH increase the actual and calculated values of pH_i. Thus, by calculation, a rise of plasma pH to 7.53–7.57 would alone account for the lower values of $^{18}F_{tw}/^{18}F_{pw}$ of both muscle and liver at 240 min with no change in pH_i, from the values obtained at the earlier time periods. The implication is that decreases of pH_i, or increases of pH_e, singly or together, could have been causally associated with the lower values of $^{18}F_{tw}/^{18}F_{pw}$ of muscle and liver at 220 and 240 min.

It is probable that the findings with one group of animals sacrificed at 220 min which gave comparatively low values of $^{18}F_{tw}/^{18}F_{pw}$ (Table II) and also those obtained with the animals sacrificed at 240 min were due to circumstances unique to these animals.[3] Speculative explanations of causes of alterations of $^{18}F_{tw}/^{18}F_{pw}$ and of pH_i and/or pH_e are potassium deficiency which elevates pH_e and lowers pH_i of muscle (14), fasting, and alterations of pulmonary ventilation. With respect to the latter, stimulation of respiration by drawing large amounts of blood may occur (15) thus elevating plasma pH and increasing transcellular pH gradients with consequent increments of plasma ^{18} levels at the expense of soft tissue levels. However, if this was the cause of the depressed $^{18}F_{tw}/^{18}F_{pw}$ ratios it would have to be assumed that hyperventilation from this cause was especially pronounced with only one group of the animals sacrificed at 220 min and those sacrificed at 240 min.

The volumes of chloride space given in Table III were derived, in the manner indicated in a footnote to the table, from the results of chloride analyses of the tissues and plasma. Very closely concordant values for chloride space were obtained from the distribution of ^{35}Cl and ^{36}Cl (Table II) except, as indicated above, for tendon at 80 min.

The fluid space volumes (Table III) and the ratios of $^{18}F_{tw}/^{18}F_{pw}$ (Table II) were used to calculate intracellular fluid fluoride concentrations of liver and muscle as percentages of that of plasma water at each of the time periods as

$$\frac{(^{18}F_{tw}/^{18}F_{pw} \times F_{pw} \times TW) - (F_{pw} \times ECF)}{F_{pw} \times ICF} \times 100,$$

where F_{pw} is the $[F^-]$ of plasma water and TW, ECF, and ICF are, respectively, the volumes in liters/kg tissue, of total water, chloride space, and intracellular fluid.[4] The use of this equation assumes that $^{18}F_{tw}/^{18}F_{pw}$ equals $^{19}F_{tw}/^{19}F_{pw}$ which is valid when $^{18}F_{tw}/^{18}F_{pw}$ has a stable value over time.

The numerical values for intracellular fluoride concentrations in Table III were obtained by use of the expression given above and an assigned value of $[F^-]_{pw}$. Since the actual value of $[F^-]_{pw}$ does not affect the results expressed as percentages

[3] The replicate results for $^{18}F_{tw}/^{18}F_{pw}$ for liver at 220 min were significantly different, $P < 0.05$ and > 0.01, and those for muscle at the same time approached but did not attain significance at the 0.05 level. The other replicate results for $^{18}F_{tw}/^{18}F_{pw}$ did not vary significantly from the overall mean result at the same time period.

[4] $[F]_{pw}$ in the second term of the numerator of the expression is not multiplied by some number greater than 1.0 (e.g., 1.05) as would be required if a Donnan membrane effect on fluoride ion were fully exhibited between plasma and interstitial fluid because of our results (1) from ultracentrifugation of plasma containing ^{18}F through collodion membranes. Constitutients of plasma hinder diffusion of fluoride and this effect is opposite in sign to that of the Donnan membrane effect. The overall result is that under physiological conditions a plasma ultrafiltrate is not markedly different in fluoride content from that of plasma water. At pH 7.4 the nonultrafilterable ^{18}F of plasma was 0.9%. The expression simplifies to: $[(^{18}F_{tw}/^{18}F_{pw} \times TW) - (ECF] \times 100/ICF$.

these may be used to estimate intracellular fluoride concentrations of liver and muscle of rats from plasma water and plasma ionic fluoride determinations.

The intracellular fluoride concentrations given in Table III are those for uniform distribution of fluoride through the entire cell waters. The influence of the reduced $^{18}F_{tw}/^{18}F_{pw}$ ratios of liver and muscle at the later times, from whatever cause they were produced, is exhibited by corresponding reductions of derived intracellular fluoride concentrations.

The lower intracellular fluoride concentration of muscle compared with that of liver is probably a consequence of the lower intracellular pH of muscle. By use of the average values of $^{18}F_{tw}/^{18}F_{pw}$ ratios over all time periods and the equation of Irvine, Saunders, Milne, and Crawford (14) the calculated mean pH_i of liver is 7.29 and that of muscle 6.97. These values of pH_i are consistent with those determined by DMO distribution: liver 7.38 (4) and 7.17 (16) and muscle 6.94 (14) and 6.92–7.01 (17).

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