Factors affecting distribution of iodide in brain and cerebrospinal fluid[1]

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REED, DONAL J, DIXON M. WOODBURY, LYLE JACOBS, AND RUSSEL SQUIRES. *Factors affecting distribution of iodide in brain and cerebrospinal fluid.* Am. J. Physiol. 209(4): 757–764. 1965.— The effects of acetazolamide, sodium perchlorate, ouabain, and of iodide loading on the processes controlling I^{131} and inulin-C^{14} distribution in the brain and CSF were studied in nephrectomized rats. It was observed that the first three drugs increased the concentration of both iodide and inulin in the brain and CSF after intracisternal administration of the tracers. It was concluded that acetazolamide reduced the rate of formation and flow of CSF, that perchlorate primarily decreased active iodide transport, and that ouabain slightly reduced CSF formation and flow. Iodide loading increased the CSF/plasma iodide ratio, expressed as percent (CSF iodide space), from 1.97 to 42.17, and the comparable values for brain were 2.02 and 11.76, respectively. The results suggest that the primary factors in the control of iodide distribution in the CNS are the following: *1*) an active iodide transport system between CSF and blood, *2*) limited permeability to iodide of the structures between blood and CSF and between blood and brain, and *3*) relatively free diffusion of iodide between brain and CSF.

blood-brain barrier inulin choroid plexus ouabain acetazolamide perchlorate

SINCE THE INTRODUCTION of the concept of the "blood-brain barrier," the distribution of a large number of substances in the brain and cerebrospinal fluid (CSF) has been investigated. The concentration of many substances in brain and CSF is only a small fraction of the concomitant concentration in plasma. Iodide is typical of this class of agents and has CSF/plasma ratios varying from 0.004 to 0.04 (1, 3, 8) and brain/plasma ratios from 0.018 to 0.06 (8). Based on kinetic studies of the distribution of a number of molecules and ions in the central nervous system (CNS) of rats, Reed and Woodbury (8) suggested that either active iodide transport or fluid flow through brain tissue might explain the low brain/plasma iodide ratio. A number of recent studies have provided evidence for the active transport of iodide from CSF to blood (1, 2, 4, 7, 8). Becker (1) and Welch (11, 12) suggested the choroid epithelium as a site of active transport of iodide from CSF to blood.

A comparison of iodide distribution in the CNS of control rats, of rats in which CSF production and flow have been selectively decreased, and of rats in which the iodide transport system has been blocked might establish whether fluid flow through the brain tissue or active transport is the predominant factor in controlling iodide distribution in the brain. Therefore, the effects of iodide loading and of three enzyme or transport inhibitors on CNS iodide distribution have been investigated. The results constitute the basis of this report.

The drugs employed were carrier iodide, a competitive inhibitor of iodide-I^{131} transport; acetazolamide, a carbonic anhydrase inhibitor that markedly reduces CSF flow (4, 5, 7, 10); sodium perchlorate, a "competitive inhibitor" of anion transport (13); and ouabain, an inhibitor of K transport that has been linked with iodide transport (13). The results contribute to an understanding of the role of fluid flow through brain tissue and of active iodide transport in determining iodide distribution in the CNS. They also provide further support for the proposed iodide transport system in the choroid plexus.

METHODS

Male Sprague-Dawley rats were employed in all experiments. In *experiment I*, 24 rats (190 ± 20 g) were divided into four groups of six animals each. All animals were bilaterally nephrectomized and each animal was injected intraperitoneally (ip) with 10 μc NaI^{131} and 2 μc inulin-C^{14} in 0.1 ml of isotonic NaCl solution. In addition, all the animals in each group received one of the following treatments: *1*) 10 mM/kg NaI, *2*) 5.0 mM/kg NaI and 5.0 mM/kg NaCl, *3*) 2.5 mM/kg NaI and 7.5 mM/kg NaCl,

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or 4) 10 mM/kg NaCl. Thus, every animal received a total of 10 mM/kg of NaI and/or NaCl. The solutions were administered ip and contained 2 mM of solute/ml. Four hours after nephrectomy and treatment, each animal was killed, samples of brain, muscle, and blood were taken, and radioactivity was determined.

In *experiment II*, 32 rats (200 ± 20 g) were divided into four groups of eight animals each. All the animals were treated the same as were the four groups described in *experiment I*. After 4 hr, CSF and plasma samples were taken and the radioactivity was counted.

In *experiment III*, 80 rats (200 ± 25 g) were divided into 4 groups of 20 animals each. The rats in each group were nephrectomized and immediately injected ip with 0.9% NaCl solution (control group); acetazolamide, 75 mg/rat (acetazolamide group); sodium perchlorate, 75 mg/rat (perchlorate group); or ouabain, 25 mg/kg (ouabain group). The volume of fluid administered was approximately 1 ml/rat. One hour after nephrectomy, each rat was injected with 10 μc NaI^{131} and 2 μc inulin-C^{14} in 0.1 ml of 0.9% NaCl solution. One-half of each group of rats was injected intracisternally (ic) and the remainder was injected ip. Four hours after injection of the radioactive tracers (5 hr after nephrectomy), samples of CSF, plasma, brain, and muscle were taken. The tissues were sampled 4 hr after injection of the tracers because our previous study had shown that about 2–4 hr is required to complete the rapid phase of inulin distribution in the CNS (8). The methods of nephrectomy, ic injection, and tissue sampling and preparation have been described (8).

The radioactivity was measured with a Tracerlab flow counter. The I^{131} was counted with the C^{14} radiation filtered out. The inulin-C^{14} was counted after the I^{131} had decayed (more than 8 half-lives). Appropriate corrections were made for decay and absorption.

TABLE 1. *Effect of iodide loading on mean radioactivity in counts per minute per gram or milliliter wet tissue* (±1 SE)

Dose of Iodide	Plasma	Brain	Muscle	CSF*
		Inulin		
Tracer	3,967±136	35.8±4.6	368±30	63±6
Tracer + 2.5 mEq/kg	3,801±272	37.1±2.0	359±40	137±20
Tracer + 5.0 mEq/kg	4,308±132	45.9±2.7	396±51	144±23
Tracer + 10.0 mEq/kg	4,493±56	48.9±2.7	392±20	166±29
		Iodide		
Tracer	11,307±981	229±27	1,506±152	223±21
Tracer + 2.5 mEq/kg	13,616±549	792±50	1,837±100	3,064±102
Tracer + 5.0 mEq/kg	15,417±591	1,336±58	2,126±139	5,120±57
Tracer + 10.0 mEq/kg	15,753±189	1,852±41	2,124±39	6,643±78

* Data in this table were obtained from *experiment I* except for values in the CSF column which were calculated from the data of *experiment II* by multiplying each CSF activity of *experiment II* by the corresponding plasma I/plasma II ratio.

TABLE 2. *Effect of iodide on mean I^{131} and inulin-C^{14} space* (±1 SE) *of brain, muscle, and CSF*

Dose of Iodide	Brain	Muscle	CSF
	Inulin		
Tracer	0.90±0.11	9.29±0.49	1.58±0.11
Tracer + 2.5 mEq/kg	0.97±0.02	9.44±0.68	3.60±0.51 (.05–.02)
Tracer + 5.0 mEq/kg	1.06±0.02	9.19±0.91	3.35±0.50 (.05–.02)
Tracer + 10.0 mEq/kg	1.09±0.02	8.72±0.43	3.69±0.64 (.1–.05)
Mean	1.00	9.16	
	Iodide		
Tracer	2.02±0.02	13.32±0.21	1.97±0.17
Tracer + 2.5 mEq/kg	5.82±0.19 (<.001)	13.49±0.33	22.53±0.78 (<.001)
Tracer + 5.0 mEq/kg	8.66±0.11 (<.001)	13.79±0.41	33.21±0.79 (<.001)
Tracer + 10.0 mEq/kg	11.76±0.29 (<.001)	13.48±0.27	42.17±0.73 (<.001)
Mean		13.52	

Figures in parentheses are values for *P*. Space = tissue radioactivity/plasma radioactivity × 100.

RESULTS

Iodide loading. The distribution of I^{131} and inulin-C^{14} in the tissues sampled is shown in Table 1. The numbers represent the radioactivity in counts per minute per milliliter plasma water or per gram wet tissue and are the mean values ± the standard error for each group of animals. Since there is some variability in the concentration of I^{131} and inulin-C^{14} in the plasma of the various groups, the effects of the treatment can best be seen by comparing the spaces rather than the radioactivity per unit of tissue. The term tracer space is defined as the ratio of the tissue tracer activity to the plasma water tracer activity, expressed as a percent. It is used for convenience and is not necessarily related to an anatomical space.

The tracer spaces, calculated from the data summarized in Table 1, are presented in Table 2. An examination of the space values in the upper half of Table 2 shows that varying the iodide load did not affect significantly most of the tissue inulin spaces; for the four groups the mean control brain and muscle inulin spaces were 1.00 and 9.16, respectively. The CSF inulin space, when tracer amounts of iodide were administered, was 1.58, a value in good agreement with those previously reported (8). The CSF inulin spaces of the iodide-loaded animals were slightly higher, 3.60, 3.35, and 3.69.

The effects of iodide loading on I^{131} distribution are shown in the lower half of Table 2. It is clear that, of the tissues studied, only muscle iodide-I^{131} was not affected by

TABLE 3. *Effect of ip administered acetazolamide, perchlorate, and ouabain on tissue radioactivity 4 hr after ip or ic injection of 10 μc I^{131} and 2 μc inulin-C^{14}*

Treatment	Plasma	Brain	CSF	Muscle
		Inulin		
Control				
ip	4,741±93	49±4	57±8	487±50
ic	3,446±231	6,574±665	20,340±2,810	336±30
Acetazolamide				
ip	5,078±160	61±3	108±13	496±23
ic	2,062±180	11,870±1,061	133,183±13,280	206±23
Perchlorate				
ip	4,921±259	65±7	67±5	617±45
ic	3,114±162	8,622±372	33,814±2,986	366±12
Ouabain				
ip	5,316±187	51±6	71±9	615±37
ic	3,007±208	7,579±471	53,201±3,662	313±16
		Iodide		
Control				
ip	10,192±582	185±13	172±15	1,022±83
ic	8,100±399	2,782±286	7,217±782	781±44
Acetazolamide				
ip	8,171±641	144±13	164±16	842±59
ic	5,590±299	4,747±383	53,057±4,568	650±41
Perchlorate				
ip	16,851±583	1,246±38	4,396±176	2,194±92
ic	12,061±573	7,515±479	26,730±2,000	1,616±112
Ouabain				
ip	11,008±960	197±14	216±28	1,018±63
ic	7,106±483	3,038±164	12,172±959	657±38

Values are in counts per minute per milliliter plasma water or CSF or per gram wet brain or muscle ±1 SE.

the size of the iodide load. In plasma, brain, and CSF (Table 1), the amount of I^{131} tended to increase as the size of the nonradioactive iodide load increased. That the increase in the brain and CSF iodide concentrations is not merely a reflection of the increased plasma iodide values is shown by the change in the brain and CSF iodide spaces (Table 2).

The brain iodide space of the control animals increased from 2.02 with a tracer dose of iodide to 11.76 when 10 mEq/kg of carrier iodide was given, almost a sixfold increase in the brain I^{131} space. The CSF iodide space also increased in response to the administration of carrier iodide; the CSF I^{131} space was 1.97 with a tracer dose of iodide and 42.17 with the addition of 10 mEq/kg of carrier iodide. Thus, the CSF iodide space increased about 21-fold in response to iodide loading while the brain I^{131} space increased 6-fold.

Inhibitors. The mean inulin-C^{14} radioactivity of each tissue sampled is shown in the upper half of Table 3. The comparable values for I^{131} radioactivity are given in the lower half of Table 3.

The inulin and iodide spaces derived from the data summarized in Table 3 are shown in Table 4. An examination of the inulin spaces shows that none of the drugs affected the brain inulin space following ip injection of inulin whereas all the drugs increased the brain inulin space after its ic injection. Acetazolamide increased slightly the CSF inulin space in the ip-injected group; all drugs increased the CSF inulin space when the tracer was administered ic.

Perchlorate is the only drug that altered significantly the brain iodide space after ip injection of I^{131}. However, after ic administration of the tracer, the brain iodide space was increased by all the drugs employed. The effects of the various drugs on CSF iodide space (column 2) are qualitatively similar to the effects on brain iodide space (column 1). In skeletal muscle, iodide distribution is not significantly different from inulin distribution, within any group; perchlorate was the only drug to alter both the muscle iodide and inulin spaces, compared with the controls.

DISCUSSION

The primary question that the work reported herein was designed to answer concerns the processes that are responsible for the low brain/plasma iodide ratio. Specifically, is iodide pumped out of the CSF and, if so, is the small iodide space in brain due to *1*) an iodide pump that transports iodide out of the brain, *2*) a flow of relatively iodide-free fluid from the CSF through the brain tissue into the plasma that is adequate to counter the diffusion of iodide into brain from the blood, or *3*) a combination of limited diffusion of iodide between plasma and brain and the low CSF iodide concentration attained by pumping iodide from the CSF into the blood?

If CSF flow could be reduced without appreciably altering iodide pumping and, conversely, if iodide pumping could be reduced without affecting CSF flow,

TABLE 4. *Effect of ip administered acetazolamide, perchlorate, and ouabain on tissue iodide-I^{131} and inulin-C^{14} space* (±1 SE) *4 hr after ip or ic injection of 10 μc I^{131} and 2 μc inulin-C^{14}*

Treatment	Brain	CSF	Muscle
	Inulin		
Control			
ip	1.03±0.10	1.20±0.15	10.27±1.10
ic	191±15.1	590±88.5	9.75±0.39
Acetazolamide			
ip	1.20±0.13	2.13±0.25 (.01–.001)	9.78±0.46
ic	576±68.6 (<.001)	6,459±1,018 (<.001)	9.99±0.47
Perchlorate			
ip	1.32±0.03	1.36±0.16	12.54±0.43
ic	277±11.5 (<.001)	1,086±115 (.01–.001)	11.75±0.21 (<.001)
Ouabain			
ip	0.96±0.10	1.32±0.17	11.57±0.52
ic	252±28.6 (.05–.02)	1,769±121 (<.001)	10.41±0.94
	Iodide		
Control			
ip	1.82±0.11	1.69±0.27	10.03±0.58
ic	35.3±2.47	89.1±8.7	9.64±0.15
Acetazolamide			
ip	1.76±0.03	2.01±0.17	10.30±0.37
ic	84.9±6.7 (<.001)	949±102 (<.001)	11.63±0.40 (<.001)
Perchlorate			
ip	7.39±0.18 (<.001)	26.1±0.99 (<.001)	13.02±0.46 (<.001)
ic	62.3±3.52 (<.001)	222±16.5 (<.001)	13.40±2.62 (<.001)
Ouabain			
ip	1.79±0.19	1.96±0.11	9.25±0.19
ic	42.3±3.29 (.02–.01)	171±7.21 (<.001)	9.24±0.39

Space = tissue radioactivity/plasma radioactivity × 100. If $P < .05$, the value is shown in parentheses.

it should be possible to determine the actual process from among the possibilities suggested. Based on the information available pertaining to the effects of the drugs employed, it seemed probable that the desired control of CSF flow and iodide pumping could be achieved by the use of acetazolamide, perchlorate, and ouabain.

In general, the variation found in the plasma iodide and inulin activities was expected, and can be explained by the effect of the route of administration or the effect of the inhibitors on tissues other than those of interest in this study, e.g., the thyroid gland. It seems highly unlikely that the altered distribution of the tracers in the brain and CSF can be attributed to the variation in the plasma tracer activity rather than to the direct effect of the drugs on the processes that control solute distribution in the CNS. Therefore, a comparison of the various spaces seems valid even though the plasma tracer activities were not uniform.

Inulin was included in this study to serve as an indicator of passive tracer distribution to which iodide distribution could be compared. Inulin was selected since it does not appear to enter cells and is thought not to be actively transported in the body. Thus, iodide distribution could be compared with inulin distribution in the same group of rats to detect active iodide transport and with that in the control group to evaluate the role of fluid flow and/or iodide pumping.

The problem of iodide binding by plasma and tissues is of some concern when discussing experiments of the type described above. It has been shown that the amount of I^{131} incorporated into organic molecules and released into the blood during the first 24 hr after administration of tracer I^{131} is minute (6, 8). Ionic binding of iodide ions to plasma proteins has been studied by many investigators and values from 0 to 5% have been reported, with most of the values less than 2%. The possibility of ionic binding of iodide to tissue proteins has not been as thoroughly investigated as plasma iodide binding. However, the data presented above in which the I^{131} iodide space of muscle did not change as the I^{131} specific activity was reduced suggests that iodide binding in muscle is not significant, if present. We have also shown (8) that when the brain I^{131} activity is increased to a high value by ic injection of I^{131} the brain radioactivity rapidly returns to the values obtained by ip injection of the tracer. This occurs many hours before the CSF I^{131} activity has decreased to that of the brain. If significant binding of I^{131} to brain proteins occurred, it might be expected that the decrease in brain I^{131} activity would lag behind that of the CSF and plasma but such is not the case. Thus, it appears that the iodide binding by plasma or tissues did not significantly influence the data presented or the conclusions drawn.

Iodide loading. The fact that varying the iodide load from 0 to 10 mEq/kg had only minor effects on the distribution of inulin suggests that iodide, in the dose range studied, did not affect the "blood-brain barrier"

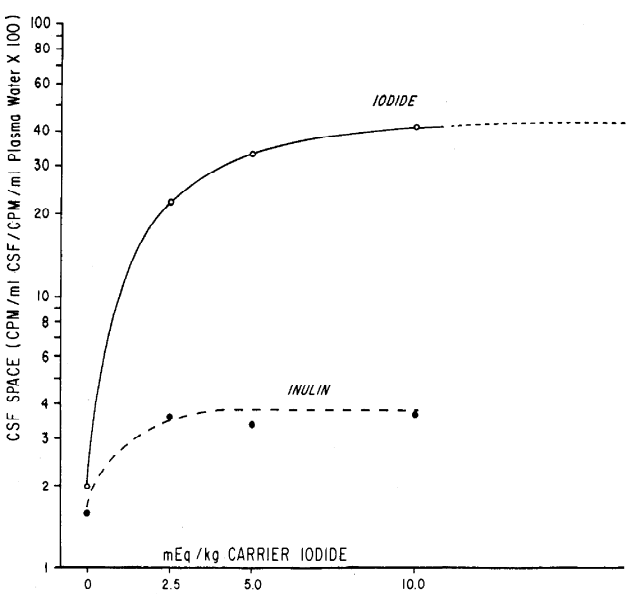

FIG. 1. CSF iodide and inulin spaces plotted semilogarithmically as a function of iodide load. A reasonable extension of the iodide curve (dotted line) is included in order to determine an asymptote for the CSF iodide curve.

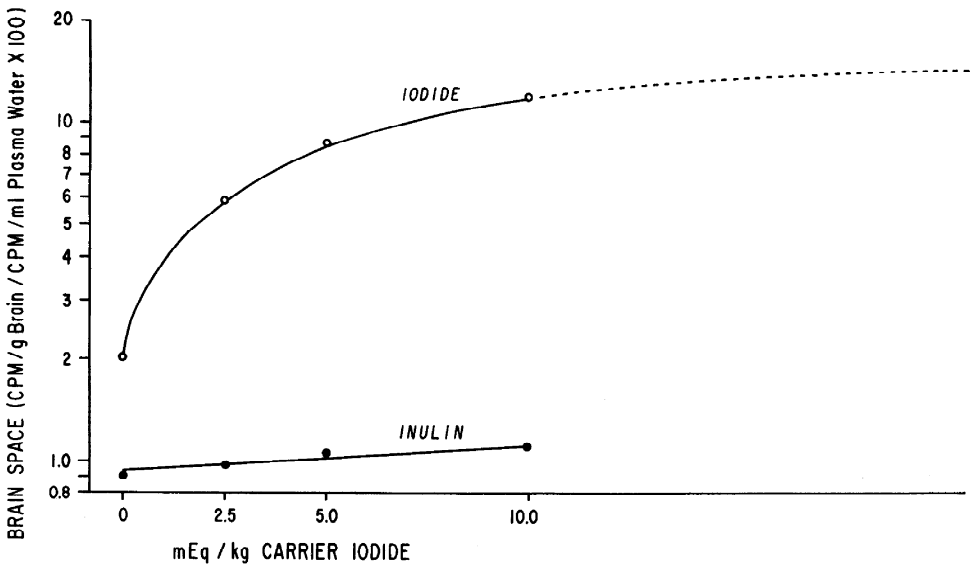

FIG. 2. Brain iodide and inulin spaces plotted semilogarithmically as a function of the iodide load. The control iodide curve has been extended beyond the last measured point (dotted line) to facilitate estimating asymptote for the brain iodide curve.

as measured by inulin distribution. Therefore, the change in brain and CSF I^{131} space must have been a direct response to the iodide load.

The values for CSF I^{131} and inulin-C^{14} spaces shown in Table 2 are plotted semilogarithmically as a function of the iodide load in Fig. 1. The reason for the slight increase in CSF inulin space in the iodide-load animals is not known; it may be due to a small decrease in the rate of CSF formation and flow in response to the iodide load. Iodide loading had little effect on the processes controlling CSF inulin concentration, as indicated by the relatively slight increase in CSF inulin space as the dose of iodide was increased. The initial point of the CSF iodide space curve (obtained with a tracer dose of iodide) is at 2% and the curve appears to approach an asymptote of about 45–50% as the iodide load is increased. This response to iodide might be due to *1*) a membrane between plasma and CSF that is normally practically impermeable to iodide and the permeability of which is increased to iodide as the size of the iodide load is increased, *2*) an active transport system for iodide with a limited capacity that removes iodide from the CSF, *3*) an increased rate of entry of iodide from brain into CSF as the iodide load is increased, or *4*) some combination of the above. Since the change in CSF inulin space in response to the iodide load was minimal, the alternatives that require membrane permeability changes in proportion to the size of the iodide load (*1* and *3*, above) seem unlikely. Although the iodide curve in Fig. 1 is somewhat different in detail from that obtained by Becker (1) in the rabbit, it is qualitatively similar. The observations presented here, when considered in conjunction with our earlier findings that ic administered iodide is removed from the CSF much faster than can be accounted for by flow through the arachnoid villi and the iodide concentration in the CSF is reduced to a value lower than that in either brain or plasma (8), strongly suggest that the low CSF/plasma iodide ratio is due to the active transport of iodide out of the CSF.

The brain iodide and inulin spaces are plotted semilogarithmically in Fig. 2, as a function of the iodide load. The curves for brain are similar in many respects to those for CSF discussed above, i.e., the iodide load had practically no effect on the inulin space of the brain whereas the iodide space increased from a minimum of about 2% to approach an asymptote (about 15%). Thus, the "leveling off" of both the CSF and brain I^{131} curves suggests the existence of one or more active transport systems that normally maintain the low brain/plasma iodide ratios and have transfer maxima.

Inhibitors. If acetazolamide acts by reducing the rate of formation of CSF without appreciably altering iodide pumping, then iodide distribution in acetazolamide-treated animals after ip injection of I^{131} should be essentially the same as in the comparable controls, since the pump would be expected to extrude the small amount of extra iodide that might diffuse into the CSF as a result of the slower flow of CSF. However, after ic injection, the reduction in CSF flow would markedly reduce the amount of iodide removed by flow through the arachnoid villi and the injected iodide would have to be removed primarily by pumping and diffusion. Consequently, the CSF iodide concentration would be much higher than the control values and be accompanied by a concomitant increase in brain iodide. After ip administration of inulin-C^{14} to the acetazolamide-treated animals, the CSF inulin concentration would be expected to increase slightly, since the time available for diffusion of inulin into the CSF would be increased by the slower rate of CSF flow, and since there appears to be no pump for the extrusion of inulin. The magnitude of the increase would be small because of the slow rate of diffusion of inulin into CSF. After ic injection, the result of the reduced CSF flow would be a large increase in the brain and CSF inulin activities inasmuch as it

has been shown by us that inulin can enter the brain from the CSF and that inulin is removed from the CSF primarily, but not entirely, by flow through the arachnoid villi (8). The data for the acetazolamide group (Table 4) are in good agreement with the results expected on the assumptions outlined above. Davson and Pollay (4) reported that acetazolamide decreased the rate of CSF formation but increased the rate of active extrusion of iodide from the CSF.

An analysis of the brain and CSF data for the perchlorate-treated animals shows marked changes in the iodide space of the ip injected group without appreciable changes in the comparable inulin spaces. Also, the ic inulin spaces increased only a small amount when compared with the changes produced by acetazolamide, suggesting that perchlorate had only a minor effect on CSF formation but primarily decreased the rate of iodide transport out of the CSF. An effect of perchlorate on permeability is not ruled out, particularly in view of the fact that both the muscle iodide and inulin spaces were increased. However, that a change in permeability can explain the CSF and brain data of the perchlorate group seems unlikely since, in muscle, both the inulin and iodide spaces were affected whereas in brain and CSF only iodide distribution was altered. Thus perchlorate must have had some selective effect on iodide transport in the CNS.

The acetazolamide and perchlorate data suggest that changes in iodide distribution in brain and CSF that are apparent after ic injection, with minimal effects after ip injection, are associated with changes in the rate of CSF formation. When the major changes in iodide distribution are seen after ip administration, then pumping appears to be the process primarily affected. Based on these criteria, ouabain would appear to have reduced the rate of formation of CSF without significantly affecting iodide transport. However, ouabain in fluid perfusing the CSF space has been found to reduce the rate of CSF formation and also of iodide transport (4). If, in the present study, the effects of ouabain had been measured earlier than 5 hr after its administration, an effect on iodide transport might have been observed.

If fluid flow from the CSF through the brain tissue does exist, it might be expected to be related to the rate of CSF formation, at least to the extent that a marked decrease in CSF formation would be accompanied by a decrease in fluid flow through the brain. Evidence that acetazolamide produced an appreciable change in CSF flow has been presented. The CSF/brain ratios for iodide and inulin for each group of ic injected animals are shown in Table 5. The ratios are related to the concentration gradient of the tracers between the CSF and brain tissue; the exact relation is dependent on the volume in which the tracers are distributed in the brain. In any case, changes in the CSF/brain ratio probably closely reflect changes in the concentration gradient between CSF and brain tissue. It can be seen that the iodide and inulin CSF/brain ratios of the ic injected control animals were 2.54 and 3.09, respectively, and the comparable values for the acetazolamide group were 11.18 and 11.21. Thus, the quantity of iodide and inulin that entered the brain compared to the amount in the CSF was only about one-fourth that of the controls. If diffusion alone is the primary factor controlling the relation of CSF and brain tracer activities, the CSF/brain ratios would be expected to remain relatively constant over a wide range of CSF tracer concentrations rather than increase by a factor of about four. Furthermore, the fact that the increase in the CSF/brain iodide and inulin ratios was nearly the same, even though the rate at which iodide and inulin diffuse across membranes has been shown to be quite different, argues against the idea that the change in ratios is due only to altered membrane permeability. The marked increase in the CSF/brain ratios of the acetazolamide group is compatible with the concept that the large decrease in the rate of CSF formation and flow contributed to a decrease in fluid flow through the brain tissue, and consequently less iodide and inulin were carried from the CSF into the brain tissue (increased CSF/brain ratios). The results with perchlorate and ouabain also tend to support the idea that fluid flow through brain tissue does exist and can effect tracer distribution under certain conditions. The CSF/brain iodide and inulin ratios of the perchlorate group, in which CSF formation was not affected appreciably, were 3.56 and 3.92 respectively, only slightly larger than the control values. In the ouabain group, where the evidence suggested there was some reduction in CSF flow, the same ratios were 4.00 and 7.02. The effect of fluid flow through the brain on tracer distribution was apparent only following ic injection of the tracers and may be of minor consequence under normal conditions.

TABLE 5. *Effect of acetazolamide, perchlorate, and ouabain on CSF/brain ratios of iodide-I^{131} and inulin-C^{14} after ic injection of tracers*

	Iodide	Inulin
Control	2.54	3.09
Acetazolamide	11.18 (<.001)	11.21 (<.001)
Perchlorate	3.56 (.3-.2)	3.92 (>.7)
Ouabain	4.00 (.1-.05)	7.02 (.05-.02)

P values are in parentheses.

General discussion. The brain, CSF, and plasma iodide concentrations appear so closely related that iodide movement and distribution in the brain can be evaluated properly only when viewed in relation to CSF and plasma iodide values. Since this relationship is so complex, a number of systems consisting of various combinations of pumps and barriers might be suggested to explain the data presented. However, an attempt will not be made to set forth all the possible combinations; rather, a single system that is relatively simple, that will explain the data, and that is amenable to experimental verification will be suggested.

The brain iodide space of about 2 % suggests that one or more of the membranes between the brain tissue and the blood are not freely permeable to iodide. If the

membranes were freely permeable to iodide, the extracellular fluid would have the same iodide concentration as plasma water. Evidence will be presented later that strongly suggests that iodide enters cells in the brain. Therefore, a brain extracellular fluid with the same iodide concentration as plasma water plus iodide inside some cells of the brain would require that the brain extracellular space be appreciably less than the 2% iodide space observed; this seems unlikely in view of the increasing body of evidence to the contrary. Thus, it seems probable that the tissues between brain and blood are only partially permeable to iodide. Previous studies (8) have shown that iodide can move rapidly across the boundary between brain and CSF. That CSF is formed, at least in part, by the choroid plexus and enters the blood stream via the arachnoid villi seems well established.

The conditions that have been outlined (an iodide pump between CSF and blood, limited diffusion of iodide from the blood into the brain and CSF, relatively free movement of iodide between brain and CSF, and CSF flow into the blood through the arachnoid villi) are adequate to explain the results presented above. Such a system is represented diagrammatically in Fig. 3. For example, under normal conditions or when a tracer dose of iodide is administered iv or ip, the CSF formed by the choroid plexus is practically devoid of iodide since the iodide is pumped out of the CSF across the choroid epithelium. Some iodide will diffuse into the brain tissue from the blood and then into the CSF, down the concentration gradient. The rate at which iodide diffuses into the brain and subsequently into the CSF, and the rate iodide leaves the CSF via flow through the arachnoid villi and by extrusion across the choroid plexus by the iodide pump are such that, in the steady state, the brain and CSF iodide spaces are about 2%. When an iodide load as large as 2.5 mEq/kg or larger is administered, the amount of iodide that enters the CSF from the brain and possibly the choroid plexus exceeds the capacity of the iodide pump, and the iodide concentration of the CSF increases (CSF iodide space increased from 1.97 to 42.17). This reduces the diffusion gradient between brain and CSF; consequently, less iodide diffuses out of the brain into the CSF and the brain iodide concentration also increases (brain iodide space increased from 2.02 to 11.76).

The fact that the asymptote approached by the CSF iodide space curve is about 45–50% (Fig. 1) instead of 100%, when the effect of the pump is minimized by the iodide load, provides evidence that the structures between plasma and CSF are not freely permeable to iodide. Thus, with the iodide pump no longer effective, the restricted diffusion of iodide into the CSF and the flow of CSF through the arachnoid villi are sufficient to maintain the CSF iodide space about one-half the value it might be expected to attain if iodide could diffuse freely into the CSF from the blood. Therefore, it would be predicted that the CSF iodide space, even with a large iodide load, would not approach 100%.

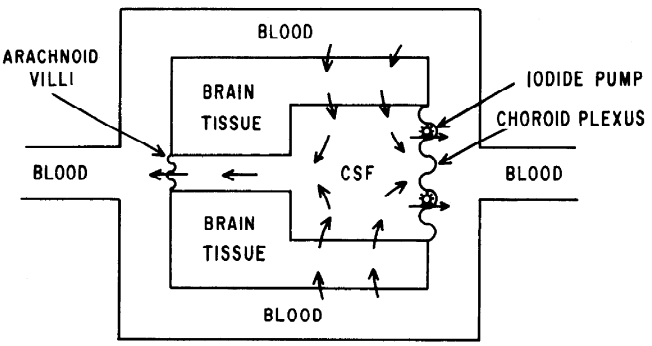

FIG. 3. Schematic representation of CNS. Arrows indicate the direction of iodide movement under normal conditions or after iv injection of a tracer dose of iodide.

Although the brain iodide space curve suggests the existence of an iodide pump with a transfer maximum for iodide, it is not necessary to postulate the existence of an iodide pump between brain and plasma or brain and CSF. Rather, the brain curve is probably a reflection of the existence of an iodide pump in the choroid plexus between CSF and plasma (see Fig. 3).

Theoretically, it would be predicted that, with the system described above, the CSF/brain iodide ratio would tend to increase as the fraction of the available iodide handled by the pump decreased, if CSF flow remained relatively constant. Furthermore, as the amount of iodide pumped out of the CSF became small compared to the total amount of iodide available to be pumped, the CSF/brain iodide ratio would become constant. From the data presented, it was calculated that the CSF/brain iodide ratio after a tracer dose of iodide was 1.0 and, with the iodide loads used, it was 3.9, 3.8, and 3.6. The theoretical predictions and the observations are in good agreement.

Information concerning iodide distribution in the brain as well as further evidence for the existence of the system suggested above for controlling CNS iodide distribution is obtained by comparing the iodide data with observations on chloride distribution in brain. It is generally accepted that the CSF chloride concentration is similar to that of plasma. Thus the brain/CSF chloride ratio is nearly the same as the brain/plasma chloride ratio, or the brain/CSF ratio expressed as a percent is the same as the brain chloride space, about 26% for the rat. It is known that the movement of chloride into and out of the brain is somewhat restricted when compared to chloride movement in muscle (9). If iodide and chloride distributions in brain tissue are similar, and if the postulated system for controlling the movement of iodide in the CNS is correct, it would be expected that, when the amount of iodide that entered the CSF was lowered by a pump, the brain/CSF iodide ratio would be higher than the comparable chloride ratio and that, when the iodide pump became relatively ineffective in reducing the iodide concentration in the CSF, the iodide and chloride brain/CSF ratios would be equal. The observed facts are that with a tracer dose of iodide

the brain/CSF ratio is 1.03, and with the three iodide loads employed (iodide pumping no longer being a significant factor) the ratios are 0.26, 0.26, and 0.28, values the same as the brain/plasma chloride ratio. Therefore, it seems likely that iodide does distribute in the various compartments in the brain in a manner similar to chloride. The iodide concentration in the extracellular fluid is probably somewhat higher than in the CSF and appreciably lower than in the plasma.

The fact that iodide appears to distribute in the brain in a manner similar to chloride would require that about one-third of the brain iodide be intracellular (9). Based on these experiments, it is concluded that the iodide space of brain, even with a high extracellular iodide concentration, does not provide a good measure of the size of the extracellular space of the brain.

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