Cerebrospinal fluid iodide[1]

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BECKER, BERNARD. *Cerebrospinal fluid iodide.* Am. J. Physiol. 201(6): 1149–1151. 1961.—In vitro preparations of rabbit choroid plexus accumulated I^{131} to a concentration 20–30 times the media. The accumulation was temperature dependent and was blocked by metabolic inhibitors. It could also be saturated with iodide, and was inhibited by perchlorate, fluoroborate, and related anions. In vivo the low 4-hr steady state concentration (1.6% of plasma) of trace doses of I^{131} in the rabbit cerebrospinal fluid was increased (to 40% of plasma) by the systemic administration of iodide or perchlorate. The results resembled qualitatively those obtained in the vitreous and aqueous humors of the same animals and suggested an active transport of iodide out of the cerebrospinal fluid, much as postulated previously for ocular fluids.

IODIDE IS TRANSPORTED ACTIVELY out of the rabbit eye and is accumulated by ciliary body-iris preparations in vitro (1). This transport process accounts for the low steady state concentrations of I^{131} in the ocular fluids. The extremely low steady state concentrations of I^{131} in the cerebrospinal fluid (2, 3) raise the question as to active transport of iodide out of the spinal fluid. The present experiments demonstrate an accumulation of iodide by rabbit choroid plexus in vitro and provide evidence for a transport of this anion out of the cerebrospinal fluid in vivo.

METHODS

In vitro. Albino rabbits weighing 2–2½ kg were killed by air embolus. Their skulls were promptly unroofed and sagittal sections made through the brain. The choroid plexus was teased out of each lateral ventricle. Each (approximately 10 mg) was incubated in 1 ml of Tyrode's solution containing approximately 0.1 μc of I^{131}. The Tyrode's solution used had the following composition (g/liter): sodium chloride, 8.0; potassium chloride, 0.2; calcium chloride, 0.2; magnesium chloride, 0.1; sodium dihydrogen phosphate, 0.05; sodium bicarbonate, 1.0; and glucose, 1.0. Before use the Tyrode's solution was adjusted to a pH of 7.45–7.50 by bubbling CO_2 through the solution and was oxygenated for 5–10 min.

Incubations were carried out with gentle shaking in a water bath at 25 C for 30 min. At the end of the incubation the choroid plexus preparations were blotted, weighed, and counted in a well-type scintillation counter. They were dried and reweighed. Counts per water content of the choroid plexus (T) were compared with the incubation fluid (M) and expressed as a T/M ratio.

In vivo. Albino rabbits weighing 2–2½ kg were pretreated with 2–3 μmoles/kg of nonlabeled sodium iodide intraperitoneally in order to minimize thyroid and plasma protein uptake of the subsequently administered I^{131}. Approximately 40 μc of I^{131} was injected intraperitoneally, and samples of plasma, anterior chamber aqueous humor, vitreous humor, and cisternal cerebrospinal fluid were obtained at various time intervals. All eye and plasma samples were obtained without anesthesia but the animals were given intravenous pentobarbital immediately prior to the cisternal taps. Samples of 100–200 μl of plasma, 200 μl of aqueous humor, and 500 μl of cerebrospinal fluid were counted in a well-type scintillation counter. Sodium perchlorate was given parenterally to some animals in doses of 3 mmoles/kg; others received nonlabeled sodium iodide in varying doses up to 20 mmoles/kg.

RESULTS

In vitro. After incubation the T/M ratio of the choroid plexus was approximately 20–30 times that of the incubation fluid. The mean value for 100 consecutive preparations was 25.6 ± 6.2 (SD). The accumulation ratio was reduced by approximately 8% per degree Centigrade decrease in temperature of incubation and reached some 15% of the 25 C value at 0 C. The reaction demonstrated this Q_{10} of approximately 2.1 up to approximately 30 C. Potassium was required in the medium, and in its absence the T/M ratio fell to less than 20% of control values. Thiouracil and acetate failed to alter the accumulation. The omission of glucose or calcium from the media had variable effects, but usually reduced the T/M ratio by 30–50%.

Received for publication 2 June 1961.
[1] This investigation was supported in part by Research Grant B-621 from the National Institutes of Health.

TABLE 1. *Concentrations of inhibitors which reduce iodide accumulation in rabbit choroid plexus in vitro by approximately 50%*

Metabolic Inhibitor	Concentration, M	Nonmetabolic Inhibitor	Concentration, M
K-strophanthin	1×10^{-7}	Perchlorate	2×10^{-6}
Digoxin	5×10^{-7}	Fluoroborate	5×10^{-6}
Iodoacetate	2×10^{-4}	Iodide (apparent K_m)	5×10^{-5}
Fluoride	6×10^{-4}	Thiocyanate	3×10^{-5}
Dinitrophenol	2×10^{-3}	Nitrate	3×10^{-3}
Malonate	5×10^{-3}	Bromide	5×10^{-2}
Cyanide	7×10^{-3}	Penicillin	1×10^{-3}
Fluoroacetate	1×10^{-2}	Iodopyracet	1×10^{-2}
		p-Aminohippurate	1×10^{-1}
		Acetazolamide	1×10^{-1}

The T/M decreased progressively with the addition of increasing amounts of nonlabeled iodide to the incubation medium. The half-saturation concentration approximated 50 μM.

The accumulation could be inhibited by suitable doses of metabolic inhibitors such as iodoacetate, cardiac glycosides, fluoride, dinitrophenol, etc. (Table 1). As has been demonstrated for thyroid slices, the inhibition by digoxin or K-strophanthin (10^{-6}–10^{-7} M) could be reversed partially by increasing the potassium in the media to 5–10 mM. Inhibitors that might compete with iodide for the transport mechanism included fluoroborate, perchlorate, and thiocyanate (Table 1). Acetazolamide, iodopyracet, penicillin, and *p*-aminohippurate decreased accumulation but only when present in high concentrations in the medium.

In vivo. In 20 rabbits the concentration of trace doses of I^{131} in spinal fluid averaged 1.6% (SD ± 0.8) of plasma values 4 hr after intraperitoneal injection. At this time the anterior chamber concentration averaged 41% (SD ± 4.3) of plasma and vitreous humor concentration 10% (SD ± 1.8) of plasma in the same animals.

Following the administration of perchlorate (3 mmoles/kg ip), the 4-hr steady state concentrations of I^{131} in the spinal fluid increased to an average of 39% (SD ± 7.5) of plasma values. Similarly, the perchlorate-treated rabbit demonstrated remarkably higher 4-hr values in the aqueous humor (85 ± SD 6.8% of plasma) and vitreous humor (29 ± SD 4.2% of plasma). The time courses of the accumulation of I^{131} in the three fluids of the perchlorate-treated rabbits are illustrated in Fig. 1.

By the intraperitoneal administration of increasing doses of nonlabeled iodide, progressive rises in steady state concentrations of I^{131} were demonstrated in cerebrospinal fluid as well as in aqueous and vitreous humors. In Fig. 1, the 4-hr steady state values for all three fluids are plotted as a function of the amount of nonlabeled iodide administered as a single dose intraperitoneally. Although increases in such steady state values were noted for spinal fluid, anterior chamber aqueous humor, and vitreous humor, each had its own saturation characteristics (Fig. 2). Interestingly, no significant increase in spinal fluid I^{131} appeared with iodide doses less than 4 mmoles/kg. At doses of 20 mmoles/kg the mean values were quite similar to those obtained 4 hr after perchlorate inhibition (Figs. 1 and 2).

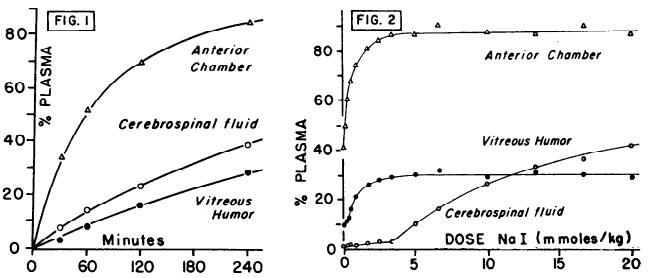

FIG. 1. Time course of accumulation of I^{131} in cerebrospinal fluid (○) and aqueous (△) and vitreous (●) humors of perchlorate-treated rabbits (3 mmoles/kg ip). Each point represents mean value for 6–10 rabbits at time indicated after injection of I^{131}.

FIG. 2. Effect of single intraperitoneal doses of sodium iodide on concentration of I^{131} in cerebrospinal fluid (○), and aqueous (△) and vitreous (●) humors. Each point represents mean value for 8–20 rabbits 4 hr after intraperitoneal administration of I^{131}.

DISCUSSION

The in vitro accumulation of iodide by the choroid plexus closely resembles that for the ciliary body-iris preparation. The T/M ratio is higher in the choroid plexus by a factor of approximately tenfold. This may relate to the fact that ciliary body-iris preparations contain much more inactive tissue. In fact, there is suggestive evidence that it is only the ciliary epithelium that accumulates iodide. The accumulations of iodide by both ciliary body and choroid plexus and their inhibitions closely resemble that of the thiouracil-treated thyroid gland, the salivary glands, and the lactating mammary gland.

The in vivo results for ocular fluids agree well with previous observations (1). They can be interpreted as a slow diffusion of iodide into the eye and an active transport out of the ocular fluids. When the transport system is saturated with iodide or inhibited by perchlorate, iodide diffuses into the eye to reach much higher steady state concentrations. The in vivo results for cerebrospinal fluid resemble those for the eye. Thus, following perchlorate administration or systemic saturation with iodide, the steady state concentration of I^{131} increases dramatically from mean values of 1.6%–40% of plasma. This also suggests a transport of iodide out of the spinal fluid as an efficient mechanism for the low steady state distribution. However, the spinal fluid findings do not rule out impermeable membranes or other forms of blood-brain barrier to iodide as an explanation for its exclusion from spinal fluid. Such a barrier could also be altered by large concentrations of iodide, perchlorate, or related anions. Active transport of iodide out of the eye has been demonstrated by measuring its rate and its capacity to act against an

opposing concentration gradient (1). Active transport of iodopyracet and related anions out of the eye and the spinal fluid have been reported (4, 5). Similar proof is needed for iodide transport out of the spinal fluid.

Both ocular and cerebrospinal fluid steady state concentrations of I^{131} are not altered by systemic iodopyracet, probenecid, or related anions, nor are the transport of these organic anions affected by the administration of iodide or perchlorate. It is probable, therefore, that the two systems are independent proccssces.

Although the in vitro data suggest the choroid plexus as one site for the assumed transport of iodide out of the spinal fluid, this by no means can be interpreted as the exclusive site of such transport. A similar situation exists in the transport of iodopyracet and related organic anions out of the cerebrospinal fluid (5). These anions are also accumulated by the rabbit choroid plexus in vitro (T/M approximately 2.5), demonstrate saturation kinetics, and are inhibited by probenecid (but not by iodide or perchlorate) in analogous fashion to renal slices and ciliary body (unpublished data). However, they may be transported out of the spinal fluid at other sites besides the choroid plexus. Similarly, in the eye it is unknown whether all of the transport of iodide or of iodopyracet out of the posterior segment of the eye takes place at the ciliary body (1, 4).

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