percent in plasma clearance of ^{36}Cl when fish were abruptly transferred to fresh water.

Perchlorate and iodide (0.14 to 0.2mM per 100 gm body weight) were also tested for an inhibitory effect on chloride efflux because of their position in the lyotropic series and their biological action to inhibit halide transport by thyroid cells. Neither sodium perchlorate (n - 5) sodium iodide (n = 3) altered chloride efflux by sea water adapted *Anguilla rostrata.*

The ratio of the concentration of chloride in sea water to that in eel plasma in the steady state is approximately 3.9 to 1 (504 mEq/L in sea water; 130 mEq/L in plasma). Thiocyanate might itself be bound and transported by the same carrier as that responsible for establishing the chloride gradient and if so the concentration of thiocyanate in the steady state should also be higher in sea water than in plasma. This was tested by injecting tracer amounts of ^{35}SCN i.p. into four eels or placing it in their sea water bath and sampling bath and plasma daily until a steady state was achieved (this occurred in 48 hours). The ratio of ^{35}SCN in sea water to that in plasma at four days averaged 3.0 (range 2.5 to 3.3), suggesting that SCN, like Cl, is actively transported outward in sea water presumably by the gill.

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THE EXCHANGE OF SEVERAL POLAR COMPOUNDS BETWEEN BLOOD, CENTRAL NERVOUS TISSUE, AND CEREBROSPINAL FLUID IN *Squalus acanthias*

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Examinations of the patterns of non-electrolyte permeability across various epithelial membrane systems such as the frog choroid plexus (J. Membrane Biol. 2: 127-149, 1970) and the rabbit gall bladder (Proc. Roy. Soc. B. 172: 227-271, 1969) have been reported. In general the rates of molecular transport increase with increasing lipid:water partition coefficients; however the smallest, most lipid-insoluble molecules (e.g., urea) cross these membranes at rates which are unusually rapid for their respective lipid solubilities. The purpose of this study was to investigate the exchange of three small organic non-electrolytes plus water between blood, central nervous tissue, and cerebrospinal fluid and to gain some information on the permeability properties of two "tight" membrane systems in the dogfish——the choroid plexus epithelium and the central nervous system (CNS) capillaries——similar to that presented for other multicellular membrane systems.

The radioactively labeled materials used in this study were ^{3}H-water, ^{14}C-urea, ^{3}H-ethylene glycol, and ^{14}C-thiourea. By a combination of intravenous and intramuscular injections constant or nearly constant plasma levels of the radioactive materials were achieved in free-swimming dogfish. Plasma samples were taken three or four times during each experiment to monitor the constancy of blood levels. Experiments in which the plasma concentrations varied by more than ± 20% from the final sample were discarded (about 50 percent of the experiments failed this test). Animals were killed from 10 minutes to 20 hours after the initial intravenous and/or intra-muscular injection(s) and samples of telencephalon (olfactory lobe), spinal cord, and CSF were rapidly obtained. Dupli-

cate samples of the two tissues, the several plasmas, and the CSF were counted by liquid scintillation spectroscopy with appropriate corrections for quenching. All of the data are presented as ratios of the various sample's radioactivity per mg or μl divided by the final plasma sample's radioactivity per μl. The water content of the tissues and CSF were determined by comparing wet and dry weights.

TABLE 1

CSF TO PLASMA DISTRIBUTION RATIOS OF FOUR LABELED COMPOUNDS AT VARIOUS TIMES AFTER SYSTEMIC INJECTION*

	10 min.	30 min.	60 min.	4 hr.	20 hr.
^{3}H-Water	.59 ± .09 (4)	-	-	-	-
^{14}C-Urea	.54 ± .03 (6)	.79 ± .03 (6)	.94 ± .02 (6)	1.02 ± .00 (2)	1.00 ± .03 (7)
^{3}H-Ethylene Glycol	.18 ± .02 (3)	.62 ± .03 (4)	.78 ± .01 (5)	1.07 ± .01 (6)	1.04 ± .03 (7)
^{14}C-Thiourea	.07 ± .01 (3)	.22 ± .02 (4)	.38 ± .02 (4)	.86 ± .02 (5)	1.02 ± .01 (4)

CSF:Plasma Water Ratio = 1.035

*Ratio = (cpm/μl CSF ÷ cpm/μl terminal plasma)
All values are given as the mean ± SE with number of determinations in parentheses

The results for the CSF and the two CNS regions are presented in Tables 1 and 2 respectively. The following relative rates of net uptake are suggested by these data: for the CSF, water = urea > ethylene glycol > thiourea; for the telencephalon, water > ethylene glycol > urea ≥ thiourea; and for the spinal cord, water > ethylene glycol ≥ thiourea > urea.

Perhaps the most unusual finding in the present study is the rapid uptake of ^{14}C-urea by the CSF, the initial rate (first 10 minutes) being very similar to that of ^{3}H-water. Since the entry of urea into CNS tissue was relatively slow most of the exchange of the compound between blood and CSF must have occurred across the choroid plexus and probably was mediated by the epithelial layer of that organ. This high permeability for urea coupled with the significantly lower permeability of ethylene glycol contrasts markedly with the results obtained by Wright and Prather for the frog choroid plexus *in vitro* (J. Membrane Biol. 2: 127-149, 1969).

The analysis of the uptake of these compounds by telencephalon and spinal cord is more difficult and will only be discussed briefly here. The CSF bathes the ventricular surface of the telencephalon and small molecular weight compounds diffuse rapidly between CSF and brain tissue. Significant net movement of urea into the brain occurs via the CSF; in contrast ethylene glycol and thiourea appear to diffuse to some extent from the brain into the CSF until both the telencephalon and the ventricular fluid have equilibrated with the blood (Cserr, Fenstermacher, Patlak, and Rall, unpublished data). Little or no such exchange occurs between the spinal cord and CSF since the

flow of CSF from the ventricular system to the spinal cord is exceedingly slow and the volume of spinal CSF relative to the spinal cord is minuscule. The interaction of the CSF with the CNS in the net transport of these compounds from blood into neural tissue probably accounts in part for the apparent differences in the uptake rates of ethylene glycol, thiourea, and urea between the telencephalon and spinal cord. Another complication with the tissue exchange analysis involves the possible binding or metabolism of the labeled thiourea by the cells of the CNS as indicated by the large ratios found at 20 hours (Table 2). A similar observation on thiourea uptake has been reported by Welch and Davson for the sciatic nerve of the rabbit (J. Neurosurg. 36: 21-26, 1972). Any comparison or analysis of the thiourea data is fraught with uncertainty without further information of the interaction of neuronal tissue with this compound.

The data presented in Tables 1 and 2 for ^{3}H-water and ^{14}C-urea can be employed to estimate the rate of blood flow to the three tissues studied. Using the Fick principle and various simplifying assumptions the following rates in ml/min-gm tissue were calculated: choroid plexus = 2.5 (based on

TABLE 2

TISSUE TO PLASMA DISTRIBUTION RATIOS OF FOUR LABELED COMPOUNDS IN TELENCEPHALON AND SPINAL CORD AT VARIOUS TIMES AFTER SYSTEMIC INJECTION*

	10 min.	30 min.	60 min.	4 hr.	20 hr.
TELENCEPHALON					
^{3}H-Water	.57 ± .05 (4)	-	-	-	-
^{14}C-Urea	.11 ± .01 (6)	.21 ± .01 (6)	.43 ± .04 (6)	.74 ± .04 (5)	.88 ± .02 (7)
^{3}H-Ethylene Glycol	.11 ± .03 (3)	.39 ± .01 (5)	.60 ± .04 (5)	.90 ± .02 (6)	.85 ± .01 (7)
^{14}C-Thiourea	.05 ± .00 (3)	.16 ± .01 (4)	.36 ± .01 (4)	.83 ± .02 (5)	1.05 ± .02 (4)
SPINAL CORD					
^{3}H-Water	.35 ± .05 (4)	-	-	-	-
^{14}C-Urea	.04 ± .01 (6)	.06 ± .00 (3)	.10 ± .02 (2)	.27 ± .01 (3)	.61 ± .03 (4)
^{3}H-Ethylene Glycol	.05 ± .01 (3)	.18 ± .02 (2)	.27 ± .02 (3)	.66 ± .04 (4)	.71 ± .02 (4)
^{14}C-Thiourea	.03 ± .00 (3)	.11 ± .01 (4)	.22 ± .02 (3)	.60 ± .03 (4)	.92 ± .02 (4)

Telencephalon:Plasma Water Ratio = 0.90

Spinal Cord:Plasma Water Ratio = 0.75

*Ratio = (cpm/mg tissue ÷ cpm/μl terminal plasma). All values are given as the mean ± SE with the number of determinations in parentheses.

water and urea data from Table 1); telencephalon = 0.1; and spinal cord = 0.04. The reported value for the rabbit choroid plexus (Am. J. Physiol. 205: 617-624, 1963) is comparable to the above estimate for the dogfish choroid plexus whereas the mammalian values for similar CNS regions are five to 10 times those for the dogfish (J. Appl. Physiol. 27: 296-300, 1969).

The data presented in this study suggest that a special transport system for urea exists in the choroid plexus of the dogfish but not in the capillary endothelium of the telencephalon and spinal cord. Furthermore estimates of blood flow to these tissues indicate that the choroid plexus is perfused at a surprisingly high rate and that the neural tissue is perfused at a much lower rate.

ACKNOWLEDGEMENTS

The authors thank Ms. Leslie Hogben for her careful calculations of the data.

1973 #15

GILL PERMEABILITY TO LIPID-INSOLUBLE MACROMOLECULES IN THE DOGFISH *Squalus Acanthias*

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Previous observations (Pietra, G.G. et al. Science 166:1643, 1969; Schneeberger, E.E. and Karnovsky, M.J., J. Cell Biol. 49:319, 1971) using lipid-insoluble macromolecular tracers in a variety of mammalian species have shown that the permeability of inter-endothelial junctions in the pulmonary microcirculation may be strongly modified by hemodynamic influences. Thus the minute pulmonary vessels that are normally impermeable to hemo-proteins of varying molecular weights (myoglobin, m.w. 18,000; horseradish peroxidase, m.w. 40,000; hemoglobin, m.w. 68,000; catalase, m.w. 240,000) become exceedingly permeable at high pulmonary capillary pressures. In contrast to the abrupt and striking change in permeability at high pulmonary capillary pressures is the gradual change that occurs in muscle capillaries: at normal capillary pressures myoglobin and hemoglobin traverse the inter-endothelial junctions slowly and their rate of passage increases gradually as capillary pressures are increased (Pietra, G.G. unpublished observations). Despite these differences the results on both the pulmonary and systemic microcirculations contradict the conventional concepts of rigid endothelial pores (Landis, E.M. and Pappenheimer, J.P., Handbook of Physiol., Circulation 2:961, 1963) and favor the hypothesis that capillary walls are permeated by distensible pores that can be stretched by physical (hemodynamic) or other influences (Shirley, H.A. Jr., et al. Amer. J. Physiol. 190:189, 1957).

In the present study we investigated the permeability of the microvasculature of the gills at different pressures using horseradish peroxidase and ferritin as tracers. Two major considerations prompted this investigation: the anatomical and hemodynamic similarities between the microcirculations of the gill and of the lung: the dependence of the dogfish for survival on impermeability of