1974 #26

TRANSPORT OF PURINES BY THE ISOLATED CHOROID PLEXUS OF THE DOGFISH SHARK (*Squalus acanthias*)

J. ARLY NELSON AND HELEN F. CSERR. SOUTHERN RESEARCH INSTITUTE, BIRMINGHAM, ALABAMA; AND BROWN UNIVERSITY, PROVIDENCE, RHODE ISLAND

A system for the transport of xanthine from cerebrospinal fluid (CFS) by the chorold plexus of rabbits has been postulated (Berlin, R.D., Science 163: 1194-1195, 1968). The purpose of this study was to determine if transport of xanthine occurred in the plexus of the dogfish and to determine the structural requirements for such transport -- is the carrier specific for purines?

Xanthine-2-^{14}C uptake by isolated choroid plexus was determined during 30 minutes incubation at 15-16°C in dogfish Ringer's solution containing 4.7 mg/ml glucose and oxygenated with 99% O_2:1% CO_2. The uptake was linear for 60 minutes at a medium concentration of 1 x 10^{-6}M under these conditions. Xanthine accumulation was maximal (saturated) at a level of about 100-500 µM, the maximal transport velocity being in the range of 450 µmoles/kg in 30 minutes. About one-half maximal transport velocity was observed at a concentration of 40 µM. The corresponding values reported by Berlin (Science 163:1194-1195, 1968) for the rabbit were 420 µmoles/kg and 170 µM. In similar experiments meninges and brain slices did not concentrate xanthine.

The structural specificity of the transport system was determined by measuring the degree of inhibition produced by various xanthine analogs. At a xanthine level of 1 x 10^{-6}M, inhibition by analogs when present at a 100-fold greater concentration (0.1 mM) was in the following order: marked inhibition (60 to 90 percent) thymine, hypoxanthine, uracil, guanine; moderate inhibition (30 to 40 percent) caffeine, chlorphenol red, and probenecid; no

inhibition, PAH, uric acid, theophylline, 6-thioguanine, 6-mercaptopurine, imidazole, 6-thioxanthine and adenine; and stimulation (+64 percent) cytosine. This result implies considerable structural specificity for the carrier. The presence of a 6-hydroxyl substituent appears necessary since replacement with a 6-amino (adenine) or 6-thio (6-thioxanthine) moiety results in loss of activity. Since N_1-methyl substitution (caffeine) leads to considerable loss of activity, the 6-hydroxyl substituent may be transported in the enol form. The lack of inhibition by PAH and uric acid implies a carrier distinct from that of the weak organic acid transport system in kidney tubules. In other experiments PAH-^{3}H was not accumulated by the dogfish choroid plexus. The uptake of xanthine was also inhibited about 50 percent by 0.1 mM cyanide, but was not altered at 4°C or at 37°C.

Hypoxanthine-8-^{14}C was accumulated by the isolated choroid plexus under these conditions, the tissue/medium concentration ratio being 23.5±3.8 at a level of 1×10^{-5}M. Uptake of hypoxanthine or of xanthine was not associated with conversion to metabolites, a result which suggests the absence of hypoxanthine-guanine phosphoribosyl transferase (HGPRTase) in this tissue. Absence of this enzyme was confirmed by analysis of tissue extracts.

In summary the accumulation of xanthine or of hypoxanthine by choroid plexus appears to occur by a carrier-mediated transport process. The physiological role for such a system may be to conserve purines by returning them to liver via the blood or to prevent accumulation of xanthine and hypoxanthine in CSF. Such accumulation is known to occur in patients with a particular neurological disturbance, i.e. Lesch-Nyhan Syndrome (Sweetman, L., Fed. Proc. 27:1055-1058, 1968).

(Supported by NIH Grant No. NS11050.)