Effect of Acetazolamide on Passage of Protein from Cerebrospinal Fluid to Plasma.* (26254)

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The enzyme, carbonic anhydrase has been reported in numerous parts of the central nervous system including the choroid plexus of the cat brain(1). In view of the known action of acetazolamide as a carbonic anhydrase inhibitor, one might expect acetazolamide to have an effect on CSF dynamics. Acetazolamide administration has been reported to reduce CSF formation and pressure(1,2,3). The following studies were undertaken to examine any possible effect of acetazolamide on passage of protein from CSF to plasma in dogs.

Methods. Mongrel dogs of both sexes, anesthetized with a combination of morphine and sodium pentobarbital, were used. The dogs were continued under the pentobarbital anesthesia throughout the experiment. These dogs were divided into 2 groups. The first group was a series of 8 dogs ranging in weight from 10 kg to 19.5 kg. Each dog was given ½ ml (25 μc) of radioiodinated human serum albumin (RISA-Abbott) intrathecally and 35 mg acetazolamide per kg intravenously. In addition, ureters of 3 of these 8 dogs were ligated and cut close to the kidney.

Passage of the tagged albumin from CSF into the bloodstream was then measured in controls and experimental group over a 24 hour period by monitoring the plasma for radioactivity according to a technic described previously(4). Radioactivity in the CSF at the end of 24 hours was also determined. In the 3 dogs with tied ureters the ligatures were inspected at end of experiment.

A second group of 6 dogs ranging in weight from 12.4 kg to 15.0 kg was studied by a different technic. Two ml of CSF from each dog was withdrawn from the cisterna magna and replaced with 2 ml of freshly-drawn, heparinized plasma taken from the same dog. Three of the 6 dogs received intravenous acetazolamide in a dose of 35 mg/kg at time of intrathecal plasma injection. Each of the 6 dogs was then tilted alternately head up and head down for 2 hours after which 1 ml CSF sample was taken. Total protein determinations were made on all CSF samples. Data and samples from dogs not yielding 3 successive clear CSF specimens were discarded.

Results. Data from the first group of 8 dogs indicate that acetazolamide appreciably slows normal passage of albumin from the CSF to the bloodstream. Fig. 1 shows the percentage of intrathecally injected albumin which could be demonstrated in the bloodstream at various intervals. Previously published data from 12 control dogs are also presented.

Less than half the normal amount of intrathecally injected radioactivity can be accounted for in the bloodstream after 24 hours in the dogs given acetazolamide. Data from the dogs with tied ureters showed that this decreased appearance was not an artefact due to increased urine output. The dogs with tied ureters showed even less of the intrathecally injected radioactivity in the bloodstream than those with intact ureters, but the difference is probably not significant. In the dogs with tied ureters the ligatures were seen to be intact with negligible hydroureter at end of experiment.

A comparison between amount of radioactivity left in the CSF of the control dogs and dogs given acetazolamide was made at end of experiment. A value representing total radioactivity remaining in the CSF for each dog was obtained by multiplying the counts per ml of CSF at end of experiment by the CSF volume, which was assumed to be proportional to the weight of the dog and arbitrarily set at 1 ml per kg. Thus, without knowing the exact percentage of injected radioactivity remaining in the CSF at the end of 24 hours, one could still compare the 2 groups. The dogs receiving acetazolamide were found to have from 3 to 7 times as

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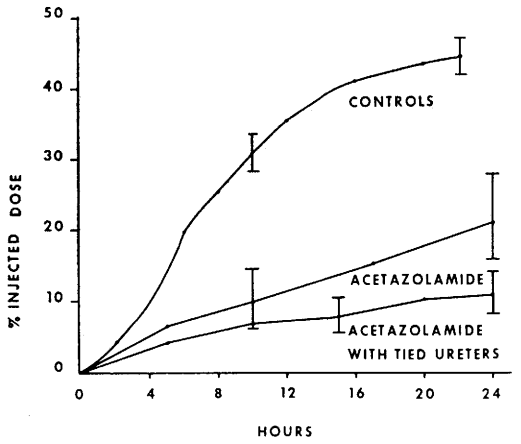

FIG. 1. Plasma radioactivity after intrathecal inj. of RISA in control dogs and dogs given a single I.V. dose of acetazolamide (35 mg/kg) simultaneously. Values represent % of intrathecal dose demonstrable in plasma ± stand. error.

much radioactivity in the CSF when compared with control dogs.

The pre-injection CSF protein level in a second group of 6 dogs was about 35 mg%. Two hours after intrathecal plasma injection the values were raised to an average of 1,000 mg% in both the untreated group and in the group receiving acetazolamide. Ten hours after injection, CSF protein levels in 3 dogs that did not receive the drug had returned to an average value of 166 mg%, while the 3 dogs given acetazolamide had average values of 875 mg%.

Discussion. We have concluded that acetazolamide slows the movement of protein from CSF to the bloodstream in the dog because bloodstream radioactivity after intrathecal RISA was diminished in dogs given acetazolamide. In addition, acetazolamide causes increased retention of CSF radioactivity in dogs given intrathecal RISA. And finally, acetazolamide retards the return to normal of artificially elevated CSF proteins. Precise explanation of the mechanisms involved in this slowing is unavailable.

The only known primary effect of acetazolamide is its ability to inhibit carbonic anhydrase(3,5). Any observed effect of acetazolamide should therefore be explained on the basis of carbonic anhydrase inhibition. Conversely, a demonstrable effect of acetazolamide on a system is presumptive evidence that the system contains carbonic anhydrase.

The assumption that carbonic anhydrase is involved in an active transport of protein from the CSF would explain the experimental results reported here. Since there is no direct evidence to support this assumption, we chose to explain our experimental findings in another manner.

Reduction by acetazolamide of CSF pressure and flow in animals has been reported (2,6). However, other studies have not been in complete agreement with these findings (7). Decrease of CSF pressures in children (1), and reduction in frequency of CSF aspiration by acetazolamide therapy in a case of hydrocephalus have also been reported(8). It has been suggested that inhibition of carbonic anhydrase at the choroid plexus and other possible secretory sites decreases the flow of CSF which is secondary to inhibition of an active chloride transport system from plasma to CSF(3).

Our interpretation is that the reduction by acetazolamide in rate of movement of protein from the CSF is secondary to a reduction in CSF flow which is necessary to keep the protein in contact with the sites of absorption. The sites of absorption are probably similar to those demonstrated in the cat(9).

Summary. Acetazolamide was shown to inhibit the passage of protein from CSF to plasma in dogs. This action was demonstrated with both normal and abnormally-elevated CSF protein levels.

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