The effect of probenecid on the elimination from CSF of intraventricularly injected 5-hydroxyindoleacetic acid in normal and hydrocephalic dogs

SIR,—In earlier investigations (Andersson & Roos, 1968 a, b) we examined the elimination of 5-hydroxyindoleacetic acid (5-HIAA) from cerebrospinal fluid (CSF) in normal and hydrocephalic dogs after intravenous injection of the precursor 5-hydroxytryptophan (5-HTP). The current investigation is a further attempt to get information about this problem using intraventricular injection of 5-HIAA with and without pretreatment with probenecid. Probenecid has been shown not only to reduce the renal excretion of 5-HIAA (Despopulos & Weissbach, 1957) but also to decrease the outflow of this acid from the brain and cerebrospinal fluid (Neff, Tozer & Brodie, 1964; Guldberg, Ashcroft & Crawford, 1966; Werdinius, 1967).

Twelve mongrel dogs of different ages were used. Hydrocephalus was induced in four dogs about two weeks before the actual investigation, using the kaolin method of Andersson (1968). The animals were kept under pentobarbitone anaesthesia during the experiments.

After puncture of a lateral ventricle, 5 μg 5-HIAA, and in one experiment 5 μg 5-hydroxytryptamine (5-HT), in 0·2 ml saline was injected. One ml of CSF was removed at regular intervals from hydrocephalic dogs by puncture of the contralateral ventricle and from normal animals by percutaneous puncture of the cisterna magna. In one hydrocephalic dog it was possible to obtain cisternal CSF at the end of the experiment. In separate experiments CSF was taken at regular intervals from the ventricle of a normal dog after an intraventricular injection of 5-HIAA and in another from the cistern after a cisternal injection. In one group (3 normal and 2 hydrocephalic dogs) the experiments were made 30 min after intravenous injection of probenecid (50 mg/kg body weight).

5-HIAA and 5-HT were determined according to Ashcroft & Sharman (1960), Roos (1963), Andén & Magnusson (1967) and Werdinius (1967).

The mean value of 5-HIAA in the ventricle of the normal dog is 0·19 $\pm$ 0·02 μg/ml (Andersson & Roos, 1968 b). Intraventricular injection of 5-HIAA to normal dogs caused a slight increase of the acid in the cisternal CSF. The highest concentration was observed in the samples taken 30 min after the injection (Fig. 1a). After pretreatment with probenecid there was a higher

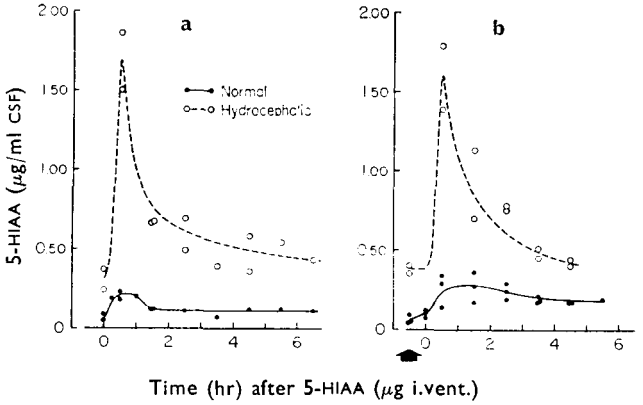

FIG. 1. CSF levels of 5-HIAA in normal (●—●) and hydrocephalic (○—○) dogs (a) after injection of 5-HIAA 5 μg, intraventricularly, (b) after probenecid, 50 mg/kg, i.v. (at arrow) given 30 min before the injection of 5-HIAA.

concentration of 5-HIAA 30 min after the injection and the return of the concentration to within normal levels did not occur over 5·5 hr (Fig. 1b).

After intraventricular injection of 5-HIAA to hydrocephalic dogs, the concentration of this acid much increased and the subsequent decrease was slow. The level of 5-HIAA 180 min after its administration was still about twice that before the injection (Fig. 1a). After pretreatment with probenecid, the 5-HIAA concentration at the various intervals was about the same as in animals which had not received probenecid (Fig. 1 b). From these data it appears that in the normal animal the elimination of 5-HIAA in CSF is reduced by probenecid; this is in agreement with earlier findings (Guldberg & others 1966; Bowers & Gerbode, 1968). In the hydrocephalic animals, however, where it has been suggested that the elimination of 5-HIAA is decreased (Andersson, 1968; Andersson & Roos, 1968 b), probenecid had no detectable influence upon the levels of this acid after intraventricular injection. If the decrease in elimination of 5-HIAA in CSF in hydrocephalus depends on some disturbance in the active transport mechanism, as suggested by Pappenheimer (1961), a mechanism sensitive to probenecid (Guldberg & others, 1966), our findings could be explained by the hypothesis that in hydrocephalus little if any of the mechanism remains for the probenecid to act upon.

The marked initial rise of the 5-HIAA after the intraventricular injection of the acid to hydrocephalic dogs together with the delayed decrease of the values, also supports the hypothesis of a decreased elimination of 5-HIAA in this condition. In one hydrocephalic dog it was possible to determine simultaneously 5-HIAA in the ventricle and in the cistern 4 hr after the injection of 5-HIAA. The finding that the concentrations were the same in both spaces again lends support to the hypothesis.

The samples were taken cisternally in the normal dogs and ventricularly in the hydrocephalic dogs. Accordingly control experiments were made (a) where 5-HIAA was injected intraventricularly to a normal dog and the concentration of the acid in the ventricular CSF followed at regular intervals and (b) where the acid was injected intracisternally and followed by determining the cisternal concentrations (Table 1). Only a moderate increase in 5-HIAA level could be detected in these two normal dogs.

TABLE 1. THE LEVEL OF 5-HIAA OVER 150 MIN IN THE CSF OF A DOG INJECTED WITH THE ACID INTRAVENTRICULARLY AND THE VENTRICULAR CSF LEVEL MEASURED, AND OF A DOG INJECTED INTRACISTERNALLY AND THE CISTERNAL CSF LEVEL MEASURED

	5-HIAA in CSF (μg/ml)			
	0 min	30 min	90 min	150 min
Dog 1 (ventr.-ventr.)	0·25	0·29	0·36	0·17
Dog 2 (cistern.-cistern.)	0·05	0·21	0·12	0·11

No 5-HT could be detected in the CSF of the normal dog. Intraventricular injection of the amine to the animal caused a slow rise in the concentration of both 5-HT and 5-HIAA in the cisternal CSF. The highest levels of both amine and acid were found in the sample taken 30 min after the injection (0·03 μg/ml for 5-HT and 0·27 μg/ml for 5-HIAA). It is apparent from this that 5-HT, penetrating into the brain tissue surrounding the ventricles (Fuxe & Ungerstedt, 1967), where the enzymes necessary for the formation of 5-HIAA are found, is rapidly eliminated from CSF, and, in agreement with earlier suggestions, the elimination of 5-HIAA is also rapid (Guldberg & others, 1966; Andersson & Roos, 1968 a).

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The effect of promethazine on the antinociceptive actions of some narcotic analgesics

SIR,—Moore & Dundee (1961) showed that the clinical effectiveness of pethidine as an analgesic was reduced when given in association with promethazine. Siker, Wolfson, & others (1966) confirmed this finding in man by tests with an ear lobe algesiometer. Moore & Dundee also reported that promethazine had a hyperalgesic effect.

Dundee (1960) and Clutton-Brock (1960) had previously found that thiopentone and pentobarbitone would reduce the effectiveness of pethidine and were hyperalgesic. Neal (1965) was able to demonstrate, in mice, a reduction of the antinociceptive activity of morphine and pethidine with thiopentone and other barbiturates. He showed also that the barbiturates were hyperalgesic in mice.

We have tried to show an antagonism of the antinociceptive action of pethidine and other analgesics in mice using an electroshock method devised by Reinhard & DeBeer and described by Burn, Finney & Goodwin (1950).

SASTO strain female mice weighing between 15 and 20 g were first tested to ensure that they would vocalize in response to electroshocks applied at 1 sec intervals to their tails. Animals which did not respond to five or fewer shocks were rejected.

Groups of ten mice were given subcutaneous injections of either saline or a solution of promethazine hydrochloride (10 mg/kg) 15 min before the subcutaneous injection of the analgesic. Thirty min later the animals were again tested for a vocalizing response to the electroshocks. Failure to respond to five more shocks than were previously required to induce a response was our