Penetration of 5-hydroxyindoleacetic acid across the blood-cerebrospinal fluid barrier

The concentration of 5-hydroxyindoleactic acid (5-HIAA) in the spinal and cisternal fluid reflects metabolism of 5-hydroxytryptamine (5-HT) in the spinal cord (Bulat & Živković, 1971) and brain tissue (Bowers, 1970) respectively, and it is used as an index of 5-HT metabolism in the central nervous system (cns). This implies that 5-HIAA in the cerebrospinal fluid (CSF) is not 'contaminated' by the 5-HIAA that is present in the blood. We have investigated whether 5-HIAA given intravenously in control and probenecid-pretreated cats can penetrate the blood-CSF and blood-cord barrier. Probenecid is known to inhibit the active transport of 5-HIAA from CSF to blood (Guldberg, Ashcroft & Crawford, 1966; Živković & Bulat, 1971).

Adult cats lightly anaesthetized with sodium thiopentone had an extradural thread ligature placed at the T_{11} segment of the spinal cord to prevent the potential mixing of spinal and cisternal fluid (Živković & Bulat, 1971). The cats were pretreated intraperitoneally with saline or probenecid (200 mg kg^{-1}). Thirty min later the saline-pretreated cats received an intravenous injection of saline or 5-HIAA (1 mg kg^{-1}), the probenecid-pretreated animals being treated similarly. Thirty min after intravenous treatment, the samples of spinal (0·5 ml) and cisternal (0·8 ml) fluid as well as the portion of spinal cord below ligature at T_{11} segment were taken for analysis of 5-HIAA (Bulat & Živković, 1971). 5-HIAA in samples of CSF and spinal cord was determined according to the modified method of Ashcroft & Sharman (1962). In some experiments 5-HIAA in the blood plasma was measured by using the modified method of Curzon & Green (1970).

Fig. 1 shows that after intravenous application of 5-HIAA (1 mg kg^{-1}) there is no change in its concentration in the spinal or cisternal fluid when compared with saline-treated cats ($P > 0{\cdot}10$). Probenecid induces an increase of 5-HIAA in the spinal fluid ($P < 0{\cdot}05$), while that in the cisternal fluid does not reach significance ($P > 0{\cdot}05$). However, if 5-HIAA is given *after* probenecid pretreatment, a striking increase of 5-HIAA in both spinal and cisternal fluid is observed in comparison with cats treated with probenecid alone ($P < 0{\cdot}01$).

Some changes of 5-HIAA in the spinal cord (Fig. 1) are similar to those observed in the spinal fluid. Thus, the concentration of 5-HIAA in the spinal cord is not

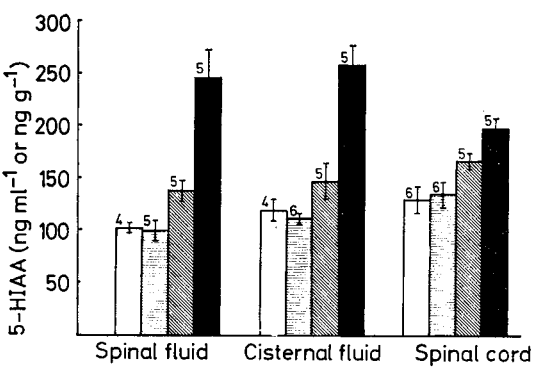

FIG. 1. Concentration of 5-HIAA in the spinal and cisternal fluid (ng ml^{-1}), and in the spinal cord (ng g^{-1}) of cats. The animals were pretreated intraperitoneally by saline or probenecid (200 mg kg^{-1}). Thirty min later the saline-pretreated cats were intravenously treated with saline (open columns) or 1 mg kg^{-1} of 5-HIAA (horizontal lines). The probenecid-pretreated animals were simultaneously given intravenous injection of saline (diagonal lines) or 1 mg kg^{-1} of 5-HIAA (solid columns). Samples of spinal and cisternal fluid and spinal cord were taken 30 min after the second injection. The values of 5-HIAA represent means ± s.e. The numbers show the number of separate experiments.

changed after the intravenous administration of this acid ($P > 0{\cdot}10$). Probenecid induces a significant increase of 5-HIAA in the spinal cord ($P < 0{\cdot}05$). However, application of 5-HIAA after probenecid does not result in a significant increase of 5-HIAA in the spinal cord compared with cats treated only with probenecid ($P > 0{\cdot}05$).

The finding that after intravenous application of 5-HIAA (1 mg kg^{-1}) no changes of 5-HIAA occurred in the spinal and cisternal fluid (Fig. 1) indicates that 5-HIAA cannot cross the blood-CSF barrier under these conditions. However, if 5-HIAA is given after probenecid pretreatment a dramatic increase of 5-HIAA in both fluids is observed (Fig. 1). This suggests that when the active transport of 5-HIAA from CSF to blood is inhibited by probenecid, penetration of 5-HIAA through the blood-CSF barrier takes place. Thus, it appears that the active transport of 5-HIAA from CSF to blood counteracts the passage of 5-HIAA from the blood to CSF. However, probenecid increases the concentration of free penicillin in the blood by competitive binding to plasma proteins (Fishman, 1966), and it may act similarly on 5-HIAA given intravenously. If this were so, increased penetration of 5-HIAA across the blood-CSF barrier may be ascribed, at least partly, to the augmented concentration of free 5-HIAA in the blood.

That 5-HIAA increases in the spinal cord after probenecid (Fig. 1) indicates that 5-HIAA is actively transported from the spinal cord to blood as was shown previously for the transport of 5-HIAA from the brain tissue to the bloodstream (Neff, Tozer & Brodie, 1967). After application of 1 mg kg^{-1} of 5-HIAA, a significant penetration of this acid across the blood-cord barrier is not found either in control or in probenecid pretreated cats (Fig. 1.). However, this does not mean that 5-HIAA cannot penetrate the blood-cord or blood-brain barrier, since after a higher dose of 5-HIAA (20 mg kg^{-1}), given intravenously, a clear-cut increase of 5-HIAA in the central nervous system was observed.

We have found that 30 min after application of 1 mg kg^{-1} of 5-HIAA intravenously the concentration of 5-HIAA is augmented more than 10 times in the blood plasma without any increase of 5-HIAA either in spinal or cisternal fluid (Fig. 1). Thus, even after great changes of 5-HIAA concentration in the blood, the level of 5-HIAA in the CSF remains constant indicating that 5-HIAA in CSF is not 'contaminated' by blood 5-HIAA. This shows that concentration of 5-HIAA in the spinal and cisternal fluid may be used as an indicator of biochemical status of 5-hydroxytryptamine neurons in the cns as was previously implied (Bulat & Živković, 1971).

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