The Transport of a Drug to the Cerebrospinal Fluid Directly from the Nasal Cavity: The Relation to the Lipophilicity of the Drug

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The objective of the present study was to clarify the relation between drug transport to the cerebrospinal fluid (*CSF*) from the nasal cavity and the lipophilicity of the drug using hydrophilic sulfonamides as model durgs. The nasal cavity of the rat was perfused in a single pass system and the concentrations of sulfonamides in plasma and *CSF* were measured. The drug concentrations in *CSF* and plasma after nasal perfusion were compared with those after intravenous (i.v.) administration. The drug concentrations in the *CSF* were remarkably high after nasal perfusion in comparison with those after i.v. administration, though the time course of the plasma concentration was not much different from that after i.v. administration. These results suggested the existence of a direct transport pathway of the sulfonamides from the nose to the *CSF*. In addition, the drug concentrations in the *CSF* increased with increasing the lipophilicity of the drugs (the partition coefficient (*Pc*) of the drugs between isoamyl alcohol and pH 7.4 phosphate buffer). A significant correlation was observed between the drug concentrations in *CSF* and *Pc*. In conclusion, the direct transport pathway of the sulfonamides from the nose to the *CSF* was confirmed and, with regard to drugs with comparatively low lipophilicity, the degree of the transport depended on its *Pc*.

Keywords nasal administration; nasal absorption; nasal cavity; cerebrospinal fluid; drug delivery; cisternal puncture; sulfonamide; lipophilicity; passive diffusion

Introduction

There exists much evidence showing the presence of a drug transport pathway from the nose to the cerebrospinal fluid (*CSF*). Kumar *et al.* have demonstrated that progesterone and estradiol achieve higher levels in the *CSF* following intranasal administration compared to intravenous (i.v.) administration.[1,2] They also showed that the concentration of dopamine in *CSF* after spraying into the nostril of rhesus monkeys was remarkably high in comparison with the concentration after i.v. administration.[3] Some physiological data shows that the cerebral perivascular space and subarachnoid space of the olfactory lobes are connected with the submucous bases of the nose.[4,5] On the basis of these reports, Pardridge suggested in his review that intranasal administration was a possible route for the delivery of a drug to the brain.[6,7] However, details of drug transport from the nasal cavity to *CSF* has been unknown. In the previous paper, we confirmed the presence of a direct transport pathway from the nasal cavity to the *CSF* using cephalexin as a model drug.[8] In this report, the transport of sulfonamides with various degrees of lipophilicity was investigated with *in situ* nasal perfusion.

Materials and Methods

Chemicals Sulfisoxazole (SIX), sulfamethizole (SMZ) and sulfisomidine (SID) were purchased from Sigma Chemical Company. Sulfanilic acid (SA) was obtained from Wako Pure Chemical Industries, Ltd. All the other chemicals were of commercially available analytical grade.

Animal Preparation Male Wistar rats weighing 220—260 g were used. The rat was anesthetized with intraperitoneal pentobarbital (50 mg/kg) and the right femoral artery was canulated with polyethylene tubing (SP-31).

Nasal Perfusion Experiment The surgical operation was carried out on the esophagus and trachea as described by Hirai *et al.*[9] The nasal cavity was perfused with an isotonic drug solution (pH 7.4 phosphate buffer, drug concentration 10 mM) at a flow rate of 1 ml/min in a single pass system. Blood was taken from the femoral artery periodically (15, 30, 45, 60 min). Sixty minutes after starting the perfusion, *CSF* was taken by cisternal puncture as previously reported.[8]

i.v. Administration Experiment Sulfonamides (SA, SMZ, SIX 1 mg/rat; SID 1.5 mg/rat) were administered intravenously *via* the left femoral vein, and plasma was collected periodically. Sixty minutes after administration, *CSF* was obtained as described above.

Partition Coefficient (*Pc*) The *Pc* was determined as previously reported using pH 7.4 phosphate buffer and isoamyl alcohol as water and organic phases, respectively.[10]

Analytical Methods Sulfonamides in *CSF* and plasma were diazotized and coupled with *N*-1-naphthyl-*N'*-diethylenediamine (Tsuda reagent) according to a standard procedure[11] with some modifications.

***CSF* and Plasma** The blood was centrifuged for 5 min and its plasma was mixed with an equal volume of 10% trichloroacetic acid for deprotenization. The mixture was recentrifuged to obtain the supernatant. Twenty microliters of 0.7 N HCl was added to 70 μl of *CSF* or a deprotenized plasma sample and then cooled to 0 °C. Ten microliters of 0.2% sodium nitrite, 20 μl of 0.2% ammonium sulfate and 10 μl of 0.2% Tsuda reagent were added and mixed well at 3 min intervals. The diazo reactants were kept at room temperature for 30 min. Twenty microliters of the reactant solution, injected with the sample injector (model 7125, Rheodyne, CA, U.S.A.), was passed into the flow cell of a spectrophotometric detector (SPD-6AV, Shimadzu) by a pump (LC-6A, Shimadzu) at a flow rate of 1.5 ml/min. The optical density of the reactant solution was recorded and analyzed by a Chromatopack (C-R2AX, Shimadzu) to obtain the concentration of the sulfonamides.

TABLE I. Chemical Structure and Partition Coefficient of Sulfonamides

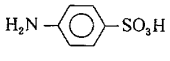
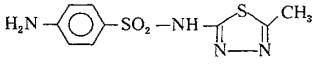
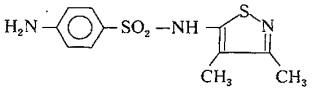
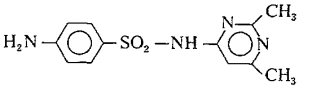
		Pc
Sulfanilic acid (SA)		0.012
Sulfamethizole (SMZ)		0.250
Sulfisoxazole (SIX)		0.261
Sulfisomidine (SID)		0.892

Table II. The Time Courses of Plasma Concentrations, *AUC* and the Concentration in *CSF* 60 min after Starting the Nasal Perfusion

Drug	Plasma (μM)				AUC_{0-60} (μM·min)	*CSF* (μM)
	15 min	30 min	45 min	60 min		
SA	2.21±0.43	5.16±0.78	8.67±1.42	12.32±1.77	333.1± 54.7	3.01±0.51
SMZ	6.79±0.50	12.46±1.63	21.52±1.95	28.08±2.34	822.1± 76.1	5.50±0.68
SIX	26.60±1.79	52.79±3.33	74.98±5.18	96.91±6.79	3042.3±200.1	6.43±1.58
SID	42.74±3.15	73.31±4.30	93.07±3.03	106.69±4.04	3959.5±124.0	9.71±0.85

Data represents mean±S.E. of 4—6 rats. AUC_{0-60} was calculated based on the linear trapezoidal rule.

Table III. The Time Courses of Plasma Concentrations, *AUC* and the Concentration in *CSF* 60 min after Intravenous Administration

Drug	Plasma (μM)				AUC_{0-60} (μM·min)	*CSF* (μM)
	15 min	30 min	45 min	60 min		
SA	25.67±2.05	15.02±1.09	11.87±1.15	8.83±1.62	1117.2± 82.9	0.640±0.082
SMZ	37.03±2.23	27.85±3.21	25.54±4.48	24.41±2.94	1873.0±153.0	0.388±0.092
SIX	85.05±2.62	69.95±3.73	65.67±2.19	63.65±1.99	4456.0±164.6	0.407±0.037
SID	116.01±3.87	100.63±4.43	84.36±4.26	80.47±1.80	6040.6±228.9	0.645±0.046

Data represents mean±S.E. of at least 3 rats. The concentration at 0 min was estimated by extrapolation of the logarithms of the plasma concentration at 15, 30, 45, and 60 min, and AUC_{0-60} was calculated based on the linear trapezoidal rule.

Results

Comparison of the Concentration in the Plasma and *CSF* after Nasal Perfusion with the Concentration after i.v. Administration The drug concentrations in plasma and *CSF* after nasal perfusion and after i.v. administration are summarized in Tables II and III, respectively. The areas under the plasma concentration–time curve (*AUC*) are also shown in Tables II and III. The concentration in *CSF* after i.v. administration was very low, and no significant difference was observed among the sulfonamides. However, the concentrations in *CSF* after nasal perfusion were remarkably high compared with those after i.v. administration, though AUC_{0-60} were high and the time courses of the plasma concentrations were not much different.

The Relation between the Lipophilicity of the Drug and Its Transfer to *CSF* Figure 1 shows the relation of the drug concentrations in *CSF* to the *Pc* of the drugs. The drug concentrations in *CSF* increased as the *Pc* of the drugs increased. A significant correlation was observed between *Pc* and the drug concentrations in *CSF* ($p<0.05$ by a Student's *t*-test).

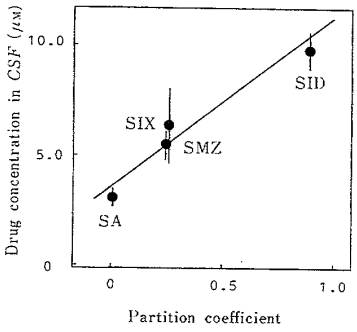


Fig. 1. The Relation of the Concentration in *CSF* to the Partition Coefficient for Sulfonamides

Each point represents the mean±S.E. of 5—7 rats. The line is the least-squares fit to data and the correlation coefficient is 0.9676.

Discussion

In the previous paper, we investigated the transport pathway of cephalexin from the nose to the *CSF* by comparing the concentrations in plasma and *CSF* after nasal, i.v. and intraduodenal administrations. The concentration of cephalexin in *CSF* 15 or 30 min after nasal administration was hundred-fold higher than the concentrations after i.v. and intraduodenal administrations, showing that there exists a direct transport pathway from the nose to the *CSF* and that the transport from the nose to the *CSF* is comparatively rapid. Kumar *et al.* showed that dopamine could be detected in the *CSF* within 15 min after nasal spraying.[3] Our finding is consistent with their results. In this paper, the existence of a direct transport pathway of the sulfonamides was also confirmed. Sulfonamides achieved remarkably higher levels in the *CSF* after nasal perfusion as compared to i.v. administration. It was also shown that the concentration in the *CSF* was the thousandth of that in the nasal perfusion fluid (10 mM). Furthermore, the degree of the drug transfer from the nose to the *CSF* was dependent on the *Pc* of the drugs. A significant correlation was observed between the drug concentration in the *CSF* and the *Pc* of the drug. However, the preliminary experiment showed that the concentration of a drug with a higher *Pc* in *CSF* after nasal perfusion was low in comparison with that expected from the relation shown in Fig. 1, showing the complexity of the drug transport from the nose to the *CSF*. This may be partly due to the rapid absorption of the drug by the systemic circulation.

In conclusion, there exists a direct transport pathway of sulfonamides from the nose to the *CSF* and, with regard to drugs with a comparatively low lipophilicity, the degree of transport was dependent on their *Pc*. In addition, the findings also provide information on the drug's side effects on the central nervous system when they are administered nasally.

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