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Direct drug transport from the rat nasal cavity to the cerebrospinal fluid: the relation to the dissociation of the drug

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Abstract—We aimed to clarify the relationship between drug dissociation (sulphisomidine) and its direct transport from the nasal cavity to the cerebrospinal fluid (CSF). Rat nasal cavities were perfused in a single pass system with buffers (pH 5·5, 6·5, 7·4, 8·7 and 9·4). Plasma and CSF were collected and the concentration of sulphisomidine was measured. Nasal clearance increased with the increase in the un-ionized fraction of the drug. The ratio of the drug concentration in CSF to that in the nasal perfusion fluid (the index of the degree of the drug transport from the nasal cavity to CSF), was changed in accordance with the un-ionized fraction of drug. These results show that both the nasal absorption and the drug transport conform to the pH partition theory.

Since the barrier function of nasal epithelium against high-molecular weight substances is poor (Hirai et al 1981), the nasal epithelium has drawn attention as a site for administration of peptide drugs (Chien 1985; Chien et al 1989). Since the end of the 19th century, much evidence has been reported indicating the connection of the nasal cavity with the cerebrospinal fluid (CSF) occupying the cerebral ventricles and the subarachnoid space (Flatau 1890; Johnson & Mims 1968; Czerniawska 1970). Some physiological data show that the cerebral perivascular space and the subarachnoid space of the olfactory lobes are connected with the submucous bases of the nose (Jackson et al 1979; Bradbury et al 1981). It was also reported by Kumar et al (1974, 1982) that when progesterone was administered nasally, it reached a higher level in CSF in comparison with that after intravenous administration. The brain capillary endothelium severely restricts the solute entry from the blood into the brain (Reese & Carnovsky 1967), the so-called blood-brain barrier (Rapoport 1976). Therefore, it is difficult to deliver hydrophilic drugs to the brain by oral or intravenous administration. However, since there exists no tight barrier between the brain and CSF, the drug may be delivered to the brain efficiently by nasal administration (Pardridge 1986). We previously reported the existence of the direct transport pathway from nasal cavity to CSF (Sakane et al 1991a) and clarified its relationship to the lipophilicity of the drug (Sakane et al 1991b). Our final goal is to develop an efficient delivery system to the brain by nasal administration. In this report, in order to obtain the basic information on the transport from nasal cavity to CSF, the relationship between the dissociation of the drug and its transport to CSF was investigated, using sulphisomidine (Fig. 1) as a model drug.

Materials and methods

Chemicals. Sulphisomidine was purchased from Sigma Chemical Company (St Louis, MO, USA). Other reagents were of analytical grade and obtained from Nacalai Tesque Inc. (Kyoto, Japan) and Wako Pure Chemical Industry, Ltd (Osaka, Japan).

Animal preparation and perfusion experiment. Male Wistar rats, 230–280 g, were used. Under pentobarbitone anaesthesia (40 mg kg^{-1}), the right femoral artery was cannulated with polyethylene tubing (SP-31) for the collection of blood samples. According to the method of Hirai et al (1981), the surgical operation was carried out on the trachea and the oesophagus. The nasal cavity was perfused with an isotonic buffer (pH 5·5, 6·5, 7·4, phosphate buffer; pH 8·7, 9·4 borate buffer) in a single pass system at a flow rate of 1 mL min^{-1} using a peristaltic pump. The drug concentrations in the perfusion fluid were 2 mM at pH 5·5, 5 mM at pH 6·5 and 10 mM at pH 7·4, 8·7 and 9·4. The blood was collected 15, 30, 45 and 60 min after starting the perfusion and at the end of experiments, CSF was obtained by cisternal puncture as previously described (Sakane et al 1991a). Since the drug concentration at each pH is different due to the decrease in solubility of sulphisomidine at pH 6·5 and 5·5, the ratio of the drug concentration in CSF to that in the nasal perfusion fluid ($R_{C/N}$) is used in this study as the index indicating the degree of the drug transport from nasal cavity to CSF.

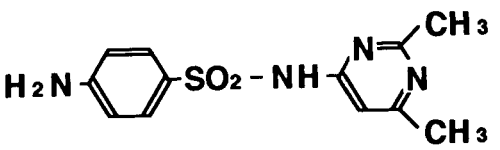

FIG. 1. Chemical structure of sulphisomidine.

Determination of nasal clearance. Sulphisomidine (1·5 mg, 5·39 μmol) was administered intravenously to rats and the time course of the concentration in plasma was measured. The elimination rate constant (k_e) and apparent distribution volume (Vd) were obtained from the plasma concentration vs time curve, assuming a one-compartment model. To determine the nasal clearance (CL_n), the time course of plasma concentration (C_p) during the nasal perfusion was fitted to the following equation by the nonlinear least-squares regression analysis program, MULTI (Yamaoka et al 1981):

$$C_p = \frac{CL_n C_n}{Vd\, k_e}(1 - e^{-k_e t})$$

where C_n and t are the concentration in the nasal perfusion fluid and the time after starting the perfusion, respectively.

Analytical procedure. The plasma was deproteinized with an equal volume of 30% trichloroacetic acid. The drug in CSF and deproteinized plasma was diazotized, coupled with Tuda reagent and determined spectrophotometrically as previously reported (Sakane et al 1991b).

Results and discussion

The plasma concentrations of sulphisomidine after intravenous administration and during nasal perfusion at pH 7·4 are shown in Fig. 2A. The elimination rate constant and the distribution volume were 0·503 h^{-1} and 41·5 mL, respectively. The concentrations in CSF at the end of experiments are also shown in Fig. 2B. The concentration in CSF after intravenous administration was small, suggesting that the cerebrovascular permeability to sulphisomidine is small. However, the concentration after nasal perfusion was remarkably high, although the area under the

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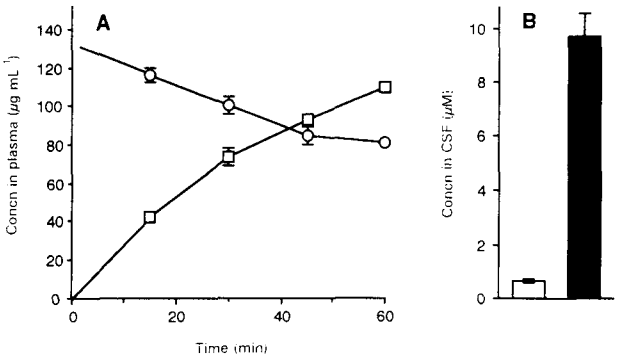

FIG. 2. Comparison of the concentrations of sulphisomidine in plasma (A) and CSF (B) after intravenous administration (○,□) and nasal perfusion at pH 7·4 (□,■). Data are expressed as the mean of 3–5 experiments ± s.e. Vd = 41·5 mL, $k_e = 0{\cdot}503\ h^{-1}$ in plasma.

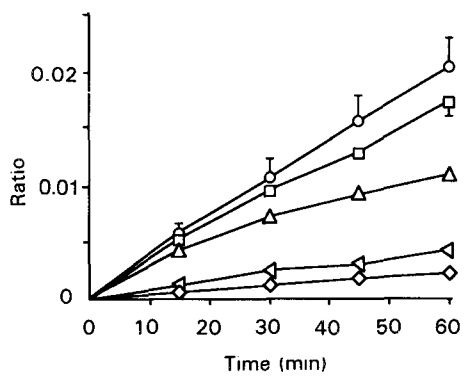

FIG. 3. The effect of pH of the nasal perfusion fluid on the time courses of $R_{P/N}$. pH values of the perfusion fluid were 5·5 (○), 6·5 (□), 7·4 (△), 8·7 (◁) and 9·4 (◇). Data are expressed as the mean of 4–7 experiments ± s.e.

plasma concentration-time curve after nasal perfusion is clearly small and the plasma concentration at the end of experiments is not so different. It was also confirmed that sulphisomidine was directly transported from the nasal cavity to CSF.

Fig. 3 represents time-courses of the ratio of the concentration in plasma to that in the nasal perfusion fluid ($R_{P/N}$). $R_{P/N}$ was large when the pH of the perfusion fluid was low. Since the pK_a value of sulphisomidine is 7·5 (Koizumi et al 1964), it is clear that the un-ionized form of the drug shows good absorption.

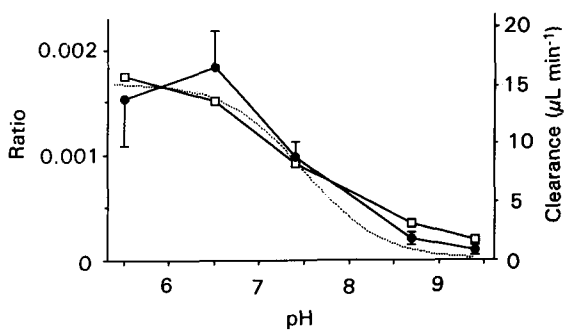

FIG. 4. Changes of $R_{C/N}$ (●) and CL_n (□) as a function of pH in the nasal perfusion fluid. The dashed line in the figure represents the pH profile of the un-ionized fraction of sulphisomidine. Data are expressed as the mean of 4–7 experiments ± s.e.

Fig. 4 shows the changes of $R_{C/N}$ and CL_n as a function of pH in the nasal perfusion fluid. $R_{C/N}$ is in the range of 10^{-3}–10^{-4}. The drug transport from nasal cavity to CSF is very rapid and the concentration in CSF is thought to reach a steady state 60 min after starting the perfusion (Sakane et al 1991a). Therefore, the concentration of drug in CSF is one thousandth of that in the nasal cavity at the steady state. The dashed line in Fig. 4 represents the pH profile of the un-ionized fraction of sulphisomidine calculated from its pK_a (Koizumi et al 1964). $R_{C/N}$ and CL_n were changed in accordance with the dissociation pattern of sulphisomidine. This result indicates that both the drug transport from the nasal cavity to CSF and the nasal absorption conform to the pH partition theory. We have already reported that the drug transport from nasal cavity to CSF is dependent on the lipophilicity of the drug (Sakane et al 1991b). Therefore, it is suggested that the drug is transported from CSF by passive diffusion.

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