Is an intranasal administration useful to drugs for central nervous system?

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Purpose

Previously, we reported that the ratio of brain AUC to plasma AUC (Kp) after intranasal (i.n.) administration tended to be higher than that after intravenous (i.v.) administration in rats, especially for low membrane permeability drugs (Pharm Res. 2019;36(5):76.).

However, the importance of the increase of brain concentration after i.n. administration in the viewpoint of pharmacological response is still unknown.

Thus, we set the following purposes:

- Evaluation of the pharmacokinetic (PK) property of drugs after i.n. administration in rats.
- Evaluation of the PK-response relationship after i.n. administration in rats using a D2 receptor antagonist.

Contents

Membrane permeability of the drugs

To investigate the pharmacokinetic property in brain after i.n. administration, several drugs with low to high membrane permeability were selected.

Therapeutic target	Compound	PAMPA (pH 7.4) permeability (nm/s)	Classification of permeability rate
5HT1B/1D agonist	Zolmitriptan	2	Low
	Rizatriptan	21	Middle
	Eletriptan	194	Middle
D2 antagonist	Risperidone	301	High

According to the previous research (Pharm Res. 2019;36(5):76.),
high membrane permeability: > 250 nm/s
low membrane permeability: < 20 nm/s
then, middle membrane permeability: 20–250 nm/s.

- PAMPA permeability values of the drugs were distributed in a wide range (2–301 nm/s).

Materials and Methods (1)

Chemicals: Zolmitriptan, Rizatriptan, Eletriptan, Risperidone

Animals: Male Crl:CD(SD) (IGS) rats, 8 weeks old (Charles River Laboratories Japan, Inc.)

All animal experiment protocols were approved by the Institutional Animal Care and Use Committee of Shonan Health Innovation Park.

Dosing regimen: i.v. (0.1 mg/kg) and i.n. (0.1 mg/kg) (cassette dosing)

Sampling time: i.v. and i.n.; 0.1, 0.25, 0.5, 1, 2 h

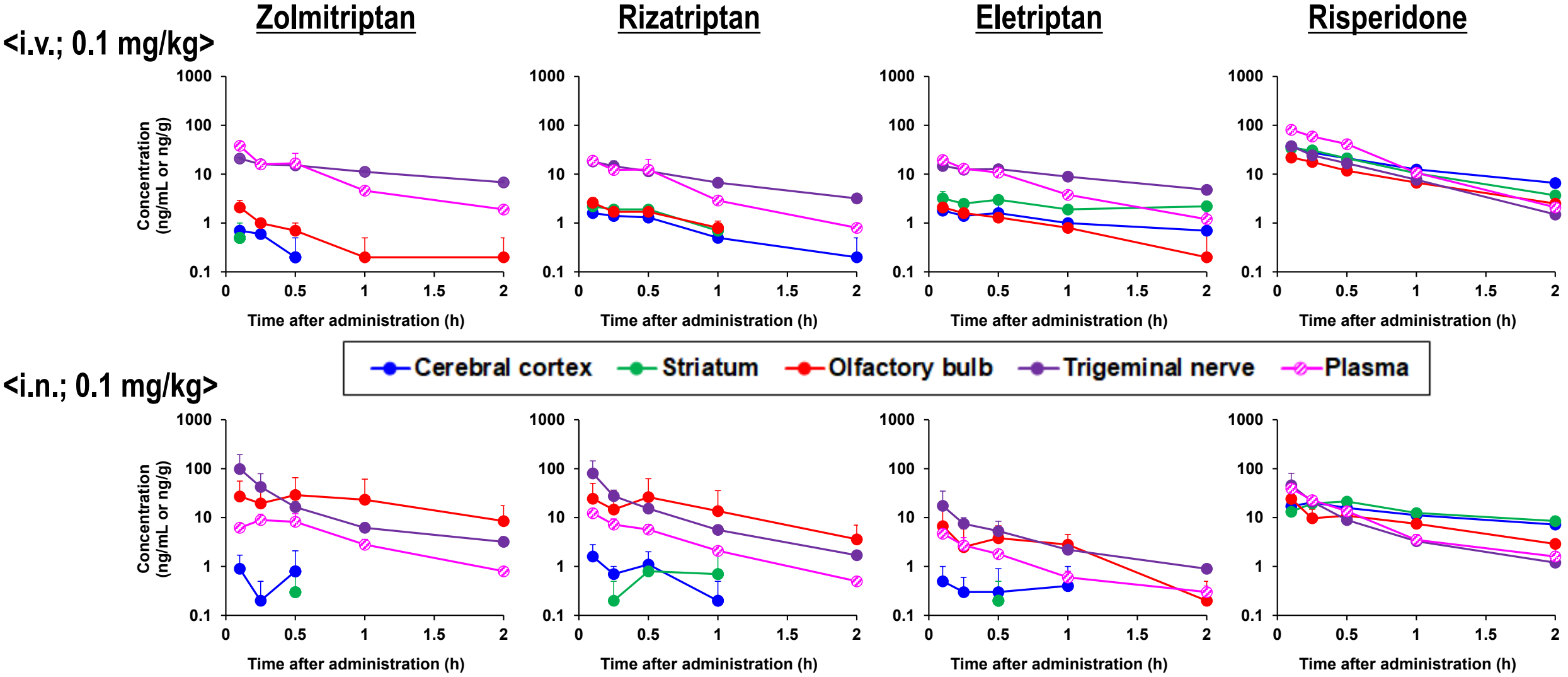
Sampling tissue: Plasma, Cerebral cortex, Striatum, Olfactory bulb, Trigeminal nerve

Bioanalysis: Determination of the drug concentration by LC/MS/MS

PK analysis:

$$Kp, ratio = \frac{Kp, brain, i.n.}{Kp, brain, i.v.} \quad \text{where} \quad Kp, brain = \frac{AUC, brain}{AUC, systemic}$$

Concentrations of the drugs in rats after i.v. and i.n. administrations



- Regarding zolmitriptan and rizatriptan, the low membrane permeability drugs, the concentration in olfactory bulb was lower than that in plasma after i.v. administration. Meanwhile, after i.n. administration the rank order reversed.

Kp ratio of the drugs in the brain regions

<Kp ratio>

$$Kp, ratio = \frac{Kp, brain, i.n.}{Kp, brain, i.v.} \quad \text{where} \quad Kp, brain = \frac{AUC, brain}{AUC, systemic}$$

Compound	Zolmitriptan	Rizatriptan	Eletriptan	Risperidone
Cerebral cortex	N.C.	1.1	<2.4	2.0
Striatum	N.C.	<0.9	<1.1	2.5
Olfactory bulb	91.4	25.4	14.6	2.5
Trigeminal nerve	3.3	2.9	2.3	1.9
PAMPA permeability (nm/s)	2	21	194	301

N.C.: Not calculated because the brain AUC at i.v. administration was not determined due to a low concentration.

- Regarding the low-to-middle membrane permeability drugs, the Kp ratios in olfactory bulb and trigeminal nerve were high, whereas those in cerebral cortex and striatum were limited.
- Regarding risperidone, the high membrane permeability drugs, the Kp ratios in cerebral cortex and striatum were higher than those of the other drugs.

Summary (1)

The pharmacokinetic property of drugs in brain after i.n. administration was evaluated.

After i.n. administration, the low-to-middle permeability drugs were more accumulated in olfactory bulb and trigeminal nerve compared with those after i.v. administration. Meanwhile, the high membrane permeability drug was evenly accumulated in all the brain regions after i.n. administration.

In the next step, we selected risperidone as a model drug for the PK-response analysis at i.n. administration. The target brain region is striatum, where a D2 receptor is highly expressed.

Contents

PK/PD/efficacy relationship for D2 receptor antagonist

Drug exposure — **Concentration of D2 receptor antagonist in striatum ⬆**

⬇

Target occupancy — D2 receptor binding of dopamine in striatum ⬇

⬇

Target engagement PD marker — cAMP ⬆, cGMP ⬆ in striatum

⬇

Downstream PD marker — ERK phosphorylation ⬆, CREB phosphorylation ⬆ in striatum

⬇

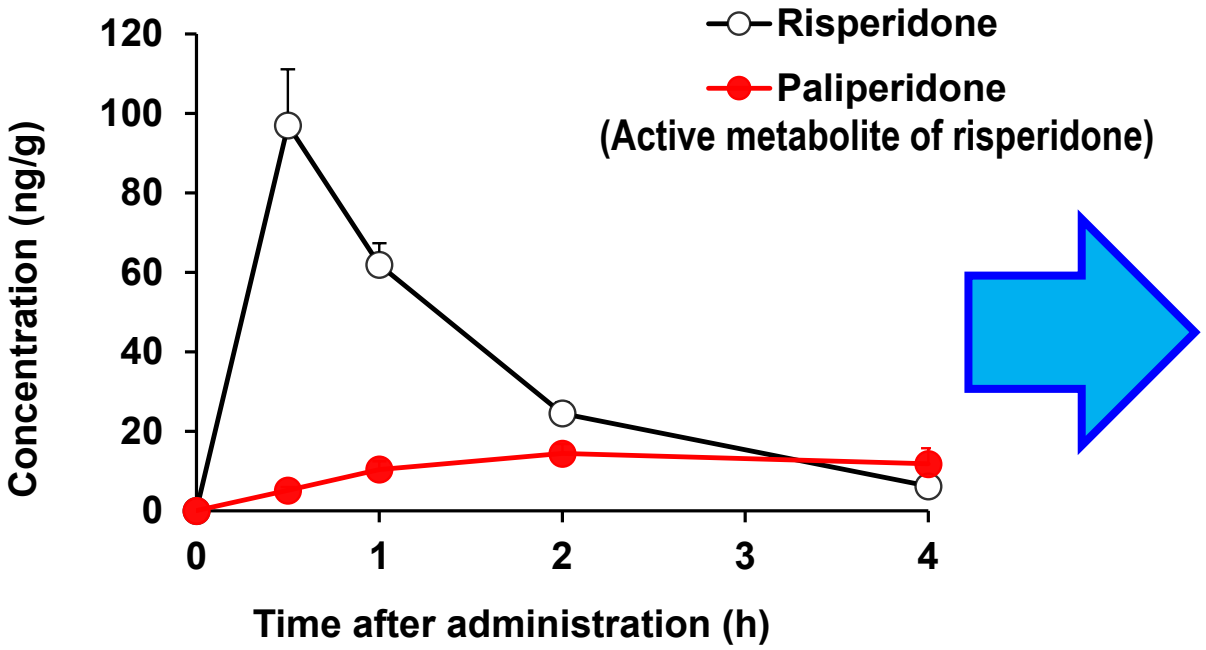
Response (efficacy, adverse effect) — Schizophrenia improvement; **Drug-induced Parkinsonism development (catalepsy)**

Materials and Methods (2)

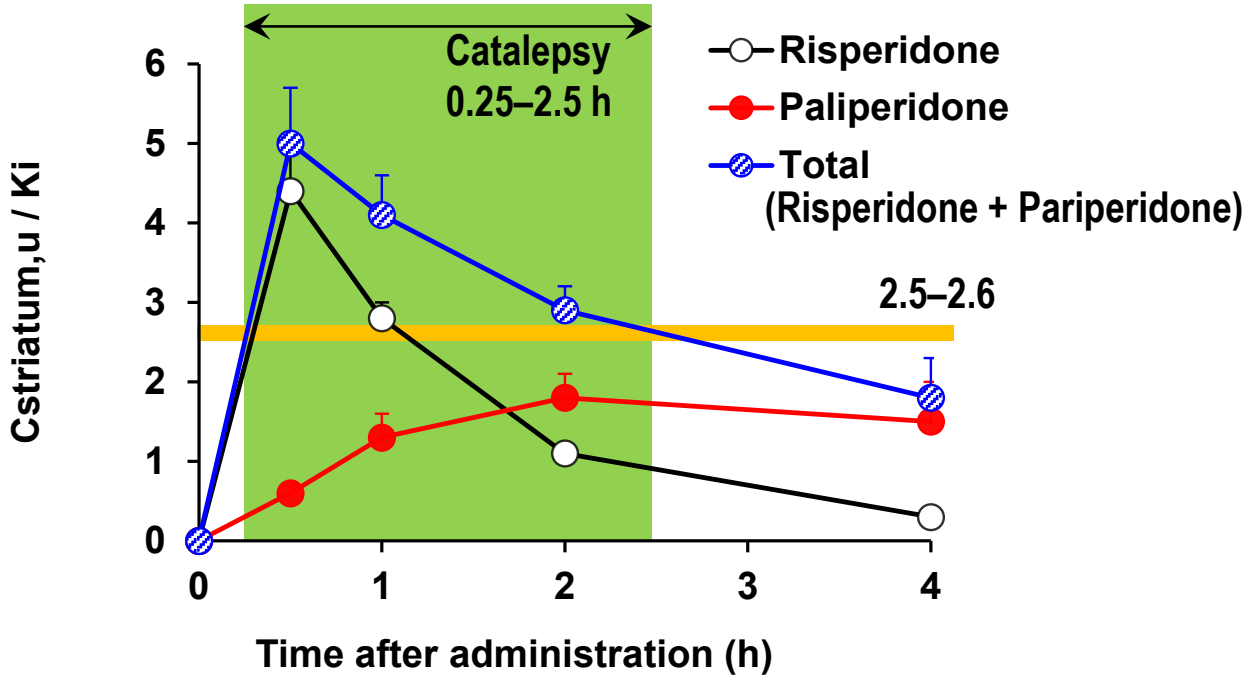
Chemicals:	Risperidone (D2 receptor antagonist)
Animals:	Male Crl:CD(SD) (IGS) rats, 8 weeks old (Charles River Laboratories Japan, Inc.)
	All animal experiment protocols were approved by the Institutional Animal Care and Use Committee of Shonan Health Innovation Park.
Dosing regimen:	Subcutaneous (s.c.) (1 mg/kg) and i.n. (1, 3, 10 mg/kg)
Sampling time:	s.c.; 0.5, 1, 2, 4 h i.n.; 0.1, 0.25, 0.5, 1 h
Sampling tissue:	Striatum
Bioanalysis:	Determination of the concentrations of risperidone and paliperidone (active metabolite) by LC/MS/MS
Physical observation:	Catalepsy (immobility)
PK-response analysis:	Relationship between unbound striatum concentration/Ki and catalepsy time

Exposure in striatum after s.c. administration (1 mg/kg)

<Concentration in striatum>



<Unbound concentration in striatum (Cstriatum,u) / Ki>



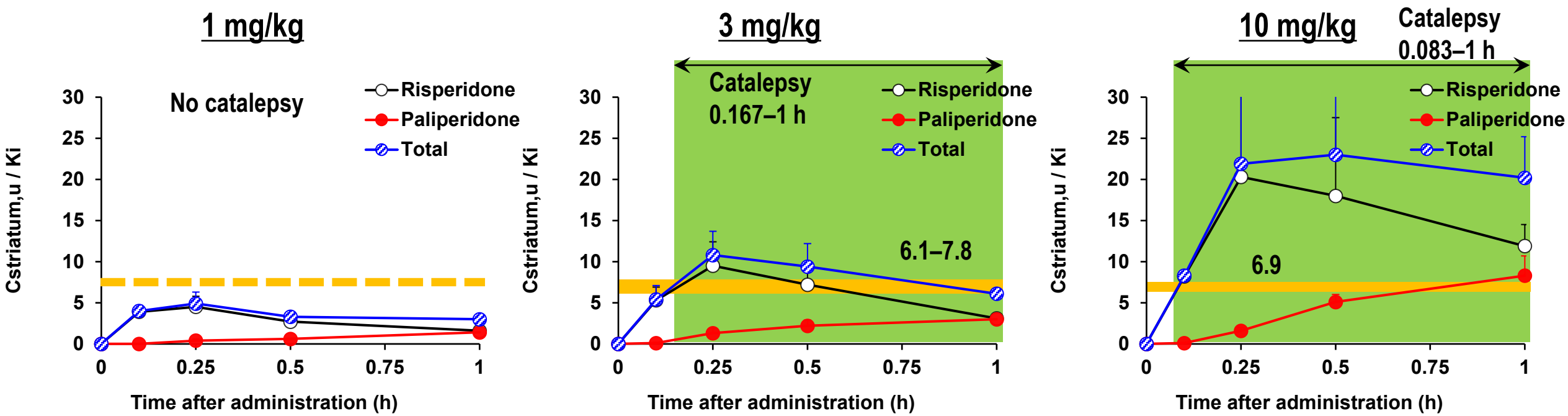
	MW	Ki (nM)	fu,brain
Risperidone	410.49	3.5	0.065
Paliperidone	426.48	2.4	0.13

Ki: Drugs R D. 2015;15(2):163-74.

- The relationship between "Cstriatum,u / Ki" and catalepsy time was suggested to be a direct response manner.
- Catalepsy was observed in the case of "Cstriatum,u / Ki" > 2–3.

Exposure in striatum after i.n. administration (1, 3, 10 mg/kg)

<Unbound concentration in striatum (Cstriatum,u) / Ki>



Risperidone: parent drug
Paliperidone: active metabolite of risperidone
Total: sum of Cstriatum,u/Ki of risperidone and paliperidone

- Catalepsy was observed in the case of "Cstriatum,u / Ki" > 6–8.
- The required "Cstriatum,u / Ki" level for catalepsy after i.n. administration would be higher than that after s.c. one.

Summary (2)

It is important to clarify whether the striatum concentration after i.n. administration is related to the pharmacological response as well as non-i.n. administration. Thus, the PK-response relationship after i.n. administration in rats was compared with that after s.c. administration using risperidone, a D2 receptor antagonist.

The results of PK-response relationship suggested that

1) the relationship between "Cstriatum,u / Ki" and catalepsy time showed a direct response manner.

2) at i.n. administration the higher striatum concentration was necessary for the pharmacological response than that at s.c. administration.

Conclusion

We evaluated the meaning of the increase of brain concentration after i.n. administration in the viewpoint of pharmacological response.

By using risperidone, the high membrane permeability drug, the relationship between the drug exposure in striatum and the pharmacological response after i.n. administration was compared with that after non-i.n. administration. At i.n. administration the higher drug exposure in striatum was necessary for the response than that at non-i.n. administration.

The results suggested that the increased drug concentration in brain after i.n. administration did not achieve a pharmacologically meaningful exposure derived from non-i.n. administration data.

As for CNS drugs, the contribution of the increase of the brain concentration after i.n. administration to the pharmacological effect would be limited.

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