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Investigation of the CNS penetration of a potent 5-HT_{2a} receptor antagonist (MDL 100,907) and an active metabolite (MDL 105,725) using in vivo microdialysis sampling in the rat

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Abstract

MDL 100,907 is a selective 5-HT_{2a} receptor antagonist which is currently being developed for the treatment of schizophrenia. Pharmacokinetic studies of MDL 100,907 in rats and dogs show that the drug is well absorbed but undergoes extensive first-pass metabolism to an active metabolite (MDL 105,725). The purpose of this study was to determine concentrations of MDL 100,907 and MDL 105,725 in the brain extracellular fluid (ECF) after administration of MDL 100,907. In vivo microdialysis sampling was used to determine the brain penetration of both parent (MDL 100,907) and metabolite (MDL 105,725). Animals ($n = 3$/dose) were given 5 i.v. and 50 mg kg^{-1} oral doses of MDL 100,907. Brain medial prefrontal cortex (mPFC) ECF concentrations were determined using microdialysis and plasma levels were determined by collecting blood samples through an indwelling cannula implanted in the jugular vein. Dialysate samples were analyzed using an LC/MS/MS assay. The data presented in this report show that the blood brain barrier (BBB) permeability of MDL 100,907 is more than four times ($4\times$) that of MDL 105,725 and that MDL 100,907 does not undergo significant metabolism to MDL 105,725 in the brain. It appears, from the data presented, that MDL 100,907 is the predominant active species present in the brain at high doses. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Schizophrenia; Microdialysis; 5-HT_{2a} receptor antagonist; Blood-brain barrier

1. Introduction

Evidence generated in the past few years has shown the importance of multiple neurochemical systems in the etiology of schizophrenia. Among the possible contributors to the symptoms of schizophrenia are the neurotransmitters dopamine (DA) and serotonin (5-HT). One theory which has been suggested is that a dysfunctional DA system plays a role in some patients and that 5-HT dysfunction plays a role in others. However, it is more likely that both systems are involved since there is a high degree of functional interaction between the systems. Recent findings show that structures within the A10 dopamine system may be influenced by the prefrontal cortex [1]. These findings suggest that increased dopaminer-

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gic activity in the prefrontal cortex can cause a corresponding decrease in activity in the A10 dopamine system. Conversely, lower dopaminergic activity in the prefrontal cortex may cause increased activity within the A10 region. These conditions may contribute to the observed positive and negative symptoms of schizophrenia. It might therefore be expected, based on the above discussion, that administration of a specific 5-HT_{2a} receptor antagonist might help to alleviate the negative symptoms of schizophrenia by increasing DA efflux in the prefrontal cortex while concurrently reducing the positive symptoms by lowering DA efflux in the A10 dopamine system. Recent data show that 5-HT_{2a} receptor antagonists such as clozapine or MDL 100,907 cause increased DA efflux in the medial prefrontal cortex [2,5]. Additionally, MDL 100,907 has been shown to reduce striatal dopamine release under conditions of 3,4-methylenedioxymethamphetamine (MDMA) induced hyper-dopaminergic activity without inhibiting the dopamine D_2 receptor. This lack of affinity for the dopamine D2 receptor and its high selectivity for the 5-HT_{2a} receptor may allow MDL 100,907 to be used as an effective treatment for both the positive and the negative symptoms of schizophrenia without the extrapyramidal side-effects associated with dopamine D2 receptor antagonists.

Pharmacokinetic studies with MDL 100,907 in rats and dogs indicate that the drug is well absorbed but undergoes extensive first-pass metabolism which significantly reduces its bioavailability. The major phase I metabolite of MDL 100,907 in animals has been shown to be 3′-*O*-demethylated MDL 100,907 (MDL 105,725) Fig. 1. This metabolite undergoes further metabolism to form sulfate and glucuronide conjugates which are excreted in urine and feces.

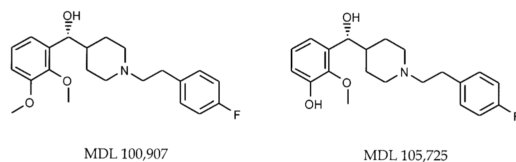

Fig. 1. Chemical structures of MDL 100,907 and the 3′-*O*-desmethyl metabolite (MDL105,725).

Although it is known that both compounds elicit CNS effects in vivo [3,4] and therefore are presumed to enter the brain, the concentration of parent drug and/or metabolite in the brain have not been previously determined. Studies have shown that the K_i for MDL 105,725 5-HT_{2a} receptor binding is from 0.45 to 2.2 nM; the corresponding value for MDL 100,907 5-HT_{2a} receptor binding is from 0.68 to 1.4 nM. As a result of the high affinity of both the parent compound and the metabolite for the 5-HT_{2a} receptor, it was essential to assess their relative CNS penetration. These data can be valuable for the determination of the importance of MDL 105,725 in terms of its contribution to the observed pharmacologic and toxicologic effects.

The objectives of the experiments described in this report were to assess the CNS penetration of MDL 100,907 in the rat following oral and i.v. administration and to further determine the ability of MDL 105,725 to cross the blood-brain barrier (BBB) and potentially contribute to the observed CNS effects. Additionally, it was of interest to determine whether MDL 100,907 could be metabolically converted to MDL 105,725 after entering the brain.

2. Materials and methods

2.1. Chemicals

MDL 100,907, MDL 105,725 and the internal standard were obtained from Hoechst Marion Roussel Research Institute (Cincinnati, OH). Acetonitrile was HPLC grade (Burdick and Jackson, Muskegon, MI). Water was purified using a NANOpure II system (Barnstead, Dubuque, IA) prior to use. The dialysis perfusate used was artificial cerebral spinal fluid (aCSF) and consisted of 2.5 mM KCl, 1.18 mM $MgCl_2$, 1.26 mM $CaCl_2$, and 125 mM NaCl. All reagents used in the preparation of buffer solutions were of analytical reagent grade or better and were used as received.

2.2. Study design

For all studies, a microdialysis probe was implanted into the medial prefrontal cortex (mPFC) and a Silastic® cannula was implanted into the right external jugular vein. The procedures and materials used are described below under animal preparation.

2.2.1. Study 1

Animals ($n = 3$) were given a 5 mg kg^{-1} i.v. dose of MDL 100,907. After dosing, plasma samples were collected at 5, 15, 30, 60, 90, 120, 180, 240, and 360 min and dialysate samples were collected every 10 min for 360 min. Both plasma and dialysate samples were analyzed for MDL 100,907 and MDL 105,725 using an LC/MS/MS method.

2.2.2. Study 2

Animals ($n = 3$) were given a 50 mg kg^{-1} oral dose of MDL 100,907. After dosing, plasma samples were collected at 15, 30, 60, 90, 120, 180, 240, and 360 min and dialysate samples were collected every 10 min for 360 min. Both plasma and dialysate samples were analyzed for MDL 100,907 and MDL 105,725 using an LC/MS/MS method.

2.3. Animals

Male Sprague–Dawley rats (Crl:CD® (SD)BR) from Charles River Laboratories, weighing between 250 and 350 g were used in these studies. Prior to and during each study, the animals were housed in a temperature and humidity controlled room with a 12-h light/dark cycle (07:00–19:00). Animals were allowed free access to food and water. The studies described in this report were conducted in accordance with the 'Principles of Laboratory Animal Care' (NIH publication # 85-23, revised 1985).

2.4. Microdialysis probe preparation

Before implantation of the microdialysis probe, the in vitro recovery was determined by placing the probe into a stirred (37°C) aCSF solution containing 50 ng ml^{-1} each of MDL 100,907 and MDL 105,725. Samples of the dialysate were collected at 10-min intervals and analyzed by LC/MS/MS to determine concentrations of MDL 100,907 and MDL 105,725. The in vitro recoveries were calculated using the expression

$$\%\,\text{Recovery}_{\text{In Vitro}} = (C_{\text{dialysate}}/C_{\text{sample}}) \times 100 \qquad (1)$$

where $C_{\text{dialysate}}$ is the concentration of analyte in the dialysate and C_{sample} is the concentration of analyte in the solution around the probe. Following insertion into the mPFC, the probe was perfused with aCSF at a flow rate of 1.0 µl min^{-1}. Prior to dosing with MDL 100,907, the in vivo delivery of the microdialysis probe was determined by perfusing the probe with a 50 ng ml^{-1} solution of MDL 100,907 and MDL 105,725 in aCSF. The in vivo recovery of the probe was then calculated (assuming that in vivo recovery is equal to delivery) using the formula

$$\%\,\text{Recovery}_{\text{InVivo}} = \text{Delivery} \times 100 \qquad (2)$$

where

$$\text{Delivery} = (C_{\text{in}} - C_{\text{out}})/C_{\text{in}} \qquad (3)$$

2.5. Animal preparation

Animals were anesthetized using a 0.2 ml/100 g body weight i.m. dose of 38 mg ml^{-1} ketamine with 2.42 mg ml^{-1} xylazine. Using aseptic surgical procedures, an indwelling Silastic® cannula (0.037″ O.D.) was implanted into the right external jugular vein and was exteriorized at the back of the neck. After implantation of the jugular cannula, the animal was placed in a stereotaxic frame (ASI Instruments) and a siliconized guide cannula (CMA/Microdialysis, Acton, MA) was inserted into the medial prefrontal cortex (mPFC) at the coordinates A 3.20 mm, M 0.80 mm, and V 4.00 mm relative to the bregma. The guide cannula was secured using dental acrylic (Sevriton) and a microdialysis probe (CMA/12, 2-mm probe length) was inserted through the guide cannula; the tip of the probe was 6.00 mm ventral relative to the bregma. After insertion of the microdialysis probe, the animal was placed in a Plexiglas containment system (CMA/120) and allowed to recover for 24 h prior to dosing with MDL 100,907.

2.6. Dose preparation and administration

For i.v. administration, a 5 mg ml^{-1} MDL 100,907 solution was prepared in a vehicle composed of 2% (w/w) citric acid, 0.6% (w/w) sodium citrate, and 0.5% (w/w) propylene glycol. A 50 mg ml^{-1} solution of MDL 100,907 was prepared in 5.1% (w/w) citric acid, 1.6% (w/w) sodium citrate, and 41.4% (w/w) propylene glycol for oral administration. Fresh dosing solutions were prepared on each day of dosing. The doses of MDL 100,907 used in these studies were chosen so that the concentrations of both parent and metabolite could be determined in the brain dialysate samples.

2.7. Sample collection

The perfusion fluid was delivered via a CMA/100 syringe pump at a flow rate of 1 ml min^{-1}. Dialysate samples were collected at 10-min intervals into 300 µl autosampler vials (Chromacol, Trumbull, CT) using a CMA/170 refrigerated sample collector set at 5°C. At the end of the study, dialysate samples were kept frozen at −20°C until analysis. Blood samples (~ 100 µl/sample) were collected through the indwelling jugular vein cannula at 5 (i.v. dose only), 15, 30, 60, 90, 120, 180, 240, and 360 min post-dose. Following each collection, the blood volume was replaced with an equal volume of normal saline through the indwelling cannula. Samples were collected into 64 × 10.25 mm heparinized Vacutainer® tubes (Becton Dickinson, Rutherford, NJ) and centrifuged at 3500 rpm (5°C) for 15 min. The resulting plasma was transferred into 1-ml microcentrifuge tubes and frozen at −20°C until analysis.

2.8. Sample analysis

Dialysate and plasma samples were analyzed using an LC/MS/MS method. Samples were injected by a Gilson Model 231 autosampler (Gilson, Middleton, WI). For the analysis of microdialysis samples, the autosampler was programmed to draw 10 µl of internal standard solution and inject into the vial containing 10 µl of microdialysis perfusate sample. The sample was mixed by the autosampler and a 10-µl aliquot was injected onto the chromatographic system. Chromatographic separations were performed using a Michrom BioResources Ultrafast Microprotein Analyzer HPLC system (Michrom BioResources, Pleasanton, CA). Following chromatographic separation, 0.127 mm I.D. PEEK tubing delivered the effluent to the electrospray ionization source of a Finnigan MAT TSQ 700 mass spectrometer (Finnigan MAT, San Jose, CA) via a Valco Instruments electric six port injector valve. This divert valve was installed to allow for automated control of the flow to the mass spectrometer.

The mobile phase consisted of acetate buffer/acetonitrile (42:58%, v/v). The aqueous buffer was prepared by adding 10 ml of glacial acetic acid and 3.85 g of ammonium acetate to 990 ml of water. The HPLC column was an Altima C8, 5 µm, 100 Å, 1 × 150 mm (Alltech, Deerfield, IL) maintained at ambient temperature with a flow rate of 60 µl min^{-1}.

For the dialysate samples, the only sample preparation required was the addition of the internal standard which was performed by the autosampler prior to injection of the sample on the LC system. Plasma samples were prepared for analysis by adding 50 µl of acetonitrile fortified with internal standard at 50 ng ml^{-1} to a 25-µl aliquot of plasma. Following the precipitation of plasma proteins, the sample was centrifuged for 10 min and the resulting supernatant was added to the autosampler vial. The methods used for plasma and dialysate sample preparation and analysis are described in detail in a separate report [6].

2.9. In vitro plasma protein binding of MDL 100,907 and MDL 105,725

Plasma protein binding of MDL 100,907 and MDL 105,725 was investigated in rat plasma using ultrafiltration (Amicon, Beverly, MA). Plasma samples were prepared at concentrations of 10, 100, and 1000 ng ml^{-1} in triplicate for both compounds. To evaluate the potential change in protein binding of each compound in the presence of the other, binding was also investigated with

Table 1
Plasma protein binding of MDL 100,907 and MDL 105,725

Concentration ($ng\ ml^{-1}$)	MDL 100,907 (% Bound ± S.D.)	MDL 105,725 (% Bound ± S.D.)	MDL100,907 and MDL 105,725 Together	
			MDL 100,907 (% Bound ± S.D.)	MDL 105,725 (% Bound ± S.D.)
10	46.7 ± 14.2	74.3 ± 4.88	NA	NA
100	57.9 ± 3.10	68.8 ± 3.66	59.9 ± 5.02	56.3 ± 2.99
1000	55.2 ± 3.52	29.7 ± 2.96[a]	NA	NA

$n = 3$ for all data.
NA, not available or not applicable.

MDL 100,907 and MDL 105,725 combined, each at a concentration of 100 ng ml^{-1}. After preparation, samples were allowed to equilibrate in a Beckman model GS-6R temperature controlled centrifuge (Beckman, Palo Alto, CA) at 37°C for 30 min prior to centrifugation. After equilibration, the samples were centrifuged at 3000 rpm for 15 min and the resulting ultrafiltrate (< 10% of plasma volume) was analyzed using LC/MS/MS to determine the unbound MDL 100,907 and/or MDL 105,725. Nonspecific adsorption was investigated by treating aqueous standards of each compound in the same manner as the plasma samples.

3. Results

3.1. In vitro and in vivo microdialysis recovery and delivery

Prior to dosing with MDL 100,907, the relative recovery of the microdialysis probe was determined both in vitro and in vivo. Calculation of brain concentrations of both MDL 100,907 and MDL 105,725 were based on the $recovery_{in\ vivo}$ which was determined after implanting the probe into the brain. Assuming that recovery in vivo is equal to delivery in vivo, the probe is calibrated by perfusing it with a solution containing the analyte and determining the concentration of the analyte delivered ($C_{in} - C_{out}$) into the tissue relative to the initial concentration (C_{in}) in the perfusion fluid. Results from in vitro delivery and recovery experiments showed that recovery of MDL 100,907 was 38.7% and delivery was 37.5%; for MDL 105,725 the recovery was 35.0% and delivery was 39.0%. These results indicate that there is no directional bias for either compound in crossing the dialysis membrane and support the assumption that in vivo recovery can be determined from in vivo delivery data. For the experiments described in this report, the in vivo delivery/recovery of MDL 100,907 and MDL 105,725 averaged 18.5 and 22.7% respectively.

3.2. In vitro plasma protein binding of MDL 100,907 and MDL 105,725

In order to attempt to relate unbound plasma concentrations of MDL 100,907 and MDL 105,725 to the unbound concentrations measured in the brain ECF, it was necessary to determine the plasma protein binding of each compound. Shown in Table 1 are the results of the binding studies for each compound separately and the effect on binding of each compound in the presence of the other. For MDL 100,907 the average plasma protein binding over the concentration range studied was 54.9% with no apparent dependence on concentration.

The average binding for MDL 105,725 over the concentration range observed in vivo was 71.6%; however, in this case there appeared to be a significant concentration dependence on binding with 74.3% bound at 10 ng ml^{-1}, decreasing to 29.7% at 1000 ng ml^{-1}. The binding of MDL 100,907 appeared to be unaffected by the presence

of MDL 105,725. However, in the case of MDL 105,725 the binding in the presence of MDL 100,907 was reduced relative to its binding in the absence of MDL 100,907.

3.3. MDL 100,907 and MDL 105,725 in plasma and brain ECF following 5 mg kg^{-1} i.v. and 50 mg kg^{-1} oral doses of MDL 100,907

Mean plasma (total drug) and brain extracellular fluid (ECF) levels of MDL 100,907 and MDL 105,725 following a 5 mg kg^{-1} i.v. dose of MDL 100,907 are shown in Fig. 2. The brain ECF levels of MDL 100,907 quickly increase following i.v. administration to reach a C_{max} of 422 ± 99 ng ml^{-1} at 32 ± 11.5 min post-dose (Table 2). After reaching the maximum concentration in the brain ECF, the rate of elimination from the brain ($t_{1/2} = 50.6 \pm 2.25$ min) is approximately the same as from plasma ($t_{1/2} = 71.3 \pm 18.1$ min), suggesting that elimination from plasma controls the rate of elimination from the brain. At this dose level, the plasma concentrations of MDL 105,725 were low relative to the concentrations of MDL 100,907 with mean AUC values of 4600 ± 1210 and $44\,200 \pm 10\,500$, respectively. Brain ECF AUC values were $28\,000 \pm 700$ for MDL 100,907 and $< 932 \pm 322$ for MDL 105,725. For MDL 105,725 the C_{max} in brain ECF was $< 6.10 \pm 1.58$ ng ml^{-1} and the in plasma was 40.5 ± 15.1 ng ml^{-1}.

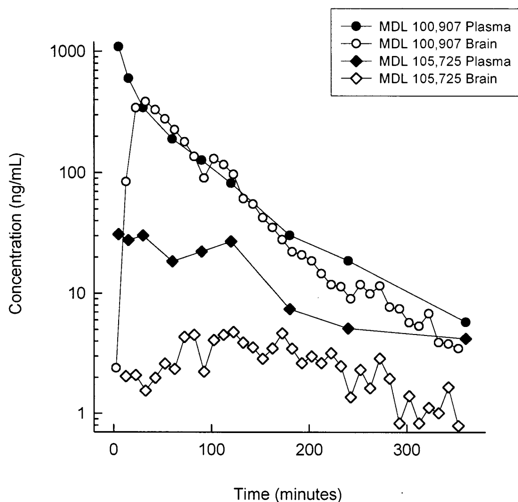

Fig. 2. Semi-logarithmic plot of mean ($n = 3$) plasma (total drug) and brain ECF concentration time profiles for MDL 100,907 and MDL 105,725 following a 5.0 mg kg^{-1} i.v. dose of MDL 100,907 to male Sprague–Dawley rats.

Following 50 mg kg^{-1} oral administration of MDL 100,907 the plasma levels of MDL 105,725 were at least double the levels of MDL 100,907 (Fig. 3Table 2). The observed T_{max} was 20.0 ± 8.66 min for MDL 100,907 and 15.0 ± 0.0 min for MDL 105,725, and the corresponding C_{max} values were 29.8 ± 20.7 ng ml^{-1} and 63.5 ± 26.8 ng ml^{-1}, respectively. Brain ECF levels of MDL 100,907 reached a maximum concentration of 26.0 ± 13.3 ng ml^{-1} at 35 min post-dose. The corresponding levels of MDL 105,725 were $< 7.8 \pm 8.4$ ng ml^{-1} at 72.5 ± 10.6 min post-dose. The brain ECF AUC for MDL 100,907 was 2280 ± 933 ng min ml^{-1}, whereas the plasma AUC was 2470 ± 1330 ng min ml^{-1}. For MDL 105,725, the brain ECF AUC was less than 877 ± 726 ng min ml^{-1} and the AUC in plasma was 6070 ± 1980 ng min ml^{-1}.

3.4. Metabolism of MDL 100,907 in the CNS

To investigate the possibility of MDL 100,907 undergoing metabolic conversion to MDL 105,725 after entering the CNS, MDL 100,907 was infused directly into the mPFC through the microdialysis probe. In this way, site specific metabolism of a compound can be evaluated without confounding the data with metabolism in tissues other than the tissue of interest. Following direct infusion of a 50 ng ml^{-1} solution of MDL 100,907 into the mPFC via the microdialysis probe, no MDL 105,725 was observed in the dialysate.

4. Discussion

The studies described in this report show that MDL 100,907 is capable of crossing the BBB more readily than MDL 105,725. After the 5 mg kg^{-1} i.v. dose of MDL 100,907 the average

Table 2
Summary of pharmacokinetic parameters

Brain data	5 mg kg^{-1} i.v. dose		50 mg kg^{-1} oral dose	
	Mean	S.D.	Mean	S.D.
MDL 100,907				
Brain data				
AUC (ng min^{-1} ml^{-1})	28 000	700	2280	933
C_{max} (ng ml^{-1})	422	99.0	26.0	13.3
T_{max} (min)	32	11.5	98.3	75.7
$t_{1/2}$ (min)	50.6	2.25	108	47.4
MRT (min)	80.9	16.4	157	37.0
Plasma data				
AUC (ng min^{-1} ml^{-1}) Total drug	44 200	10 500	2470	1330
C_{max} (ng ml^{-1}) Total drug	1480	416	29.8	20.7
T_{max} (min)	NA	NA	20.0	8.66
$t_{1/2}$ (min)	71.3	18.1	220	158
MRT (min)	59.7	4.14	267	186
MDL 105,725				
Brain data				
AUC (ng min^{-1} ml^{-1})	<932	322	<877	726
C_{max} (ng ml^{-1})	<6.10	1.58	<7.8	8.4
T_{max} (min)	125	70.7	72.5	10.6
$t_{1/2}$ (min)	131	5.66	339	165
MRT (min)	233	36.8	444	99.0
Plasma data				
AUC (ng min^{-1} ml^{-1}) Total drug	4600	1210	6070	1980
C_{max} (ng ml^{-1}) Total drug	40.5	15.1	63.5	26.8
T_{max} (min)	46.7	63.7	15	0
$t_{1/2}$ (min)	106.0	32.4	185	76.6
MRT (min)	162	38.9	279	71.6

Mean values are reported as <mean if an individual animal had undetectable levels of analyte in the brain. In this case the mean value reported is the mean of the remaining values from the individual animals.

$AUC^{MDL\ 100,907}_{Brain\ ECF}/AUC^{MDL\ 100,907}_{Plasma}$ was 0.66 ± 0.14 (mean $\pm$ S.D.) whereas following the 50 mg kg^{-1} dose the average $AUC^{MDL\ 100,907}_{Brain\ ECF}/AUC^{MDL\ 100,907}_{Plasma}$ was 1.01 ± 0.24 (Table 3). Conversely, the average $AUC^{MDL\ 105,725}_{Brain\ ECF}/AUC^{MDL\ 105,725}_{Plasma}$ was $\leq 0.25 \pm 0.13$ following the i.v. dose and $\leq 0.13 \pm 0.11$ following the oral dose.

In addition to determining the brain ECF concentrations of MDL 100,907 and MDL 105,725, it was also of interest to assess the possibility that all or part of the MDL 105,725 found in the brain was due to metabolic conversion in the CNS. Two pieces of evidence suggest that MDL 100,907 is not metabolized to MDL 105,725 after entering the brain, but MDL 105,725 crosses the BBB after being formed systemically. After perfusing the microdialysis probe with a solution containing MDL 100,907, the drug is delivered directly into the mPFC. Under these circumstances, if MDL 100,907 underwent significant metabolism to MDL 105,725 in the mPFC, it would be expected that MDL 105,725 would be observed in the perfusate samples. This was not the case. Furthermore, inspection of the relative concentrations of MDL 100,907 and MDL 105,725 in the brain following the oral and i.v. doses of MDL 100,907 also lend support to the conclusion that there is no significant metabolism of MDL 100,907 in the mPFC. After the 5 mg kg^{-1} i.v. dose of MDL 100,907, the exposure of the brain ECF to MDL

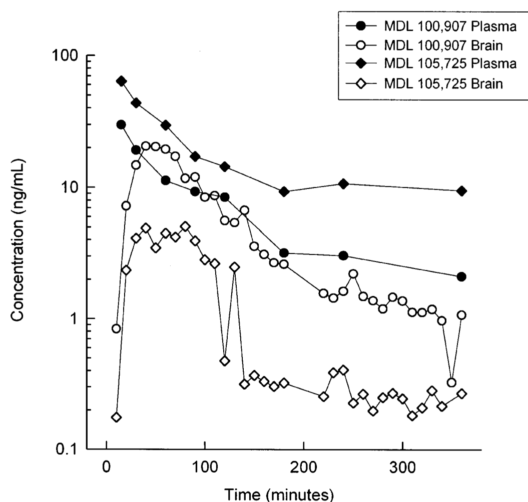

Fig. 3. Semi-logarithmic plot of mean ($n=3$) plasma (total drug) and brain ECF concentration time profiles for MDL 100,907 and MDL 105,725 following a 50.0 mg kg^{-1} oral dose of MDL 100,907 to male Sprague–Dawley rats.

100,907 is 12.3 times higher than after the 50 mg kg^{-1} oral dose (using AUC as a measure of exposure). However, the $AUC^{MDL\ 105,725}_{Brain\ ECF}$ following the i.v. dose of MDL 100,907 is approximately equal to, or slightly less than, the $AUC^{MDL\ 105,725}_{Brain\ ECF}$ following oral administration of MDL 100,907 despite the fact that the brain is exposed to a significantly greater amount of MDL 100,907 after i.v. administration. If metabolism of MDL 100,907 in the CNS contributed significantly to the observed MDL 105,725 in the brain, it would be expected that the brain concentrations would be much higher following i.v. administration of MDL 100,907 than was observed experimentally. Therefore it is concluded, based on two independent sets of data, that the MDL 105,725 which was found in the brain ECF resulted from transfer across the BBB from the systemic circulation.

Table 3
Brain to plasma AUC ratios for MDL 100,907 and MDL 105,725 following 5 mg kg^{-1} i.v. and 50 mg kg^{-1} oral doses of MDL 100,907

	AUC ratio (Brain ECF/Total plasma)
MDL 100,907	
5 mg kg^{-1} i.v.	0.66 ± 0.14
50 mg kg^{-1} oral	1.01 ± 0.24
MDL 105,725	
5 mg kg^{-1} i.v.	$<0.25 \pm 0.13$
50 mg kg^{-1} oral	$<0.13 \pm 0.11$

It is well known that a number of factors including, protein binding, BBB permeability, blood flow rate through brain capillaries, drug lipophilicity, transport mechanisms at the BBB, etc., influence the rate and extent of penetration of a drug into the brain. Although the mechanism of penetration into the brain ECF is unknown in the case of MDL 100,907 and MDL 105,725, it is likely that lipophilicity is a factor which significantly affects their penetration. This is supported by the fact that the calculated octanol/water partition coefficient (ProLogP v 4.1) for MDL 105,725 was 0.256 relative to MDL 100,907.

In conclusion, the data presented in this report shows that the brain ECF concentrations of MDL 100,907 are significantly greater ($>4\times$) than those of MDL 105,725. In addition, it was shown by comparing AUC values of each compound after oral and i.v. administration of MDL 100,907, that MDL 100,907 does not appear to be metabolized to MDL 105,725 in the brain. It then follows that both MDL 100,907 and MDL 105,725 enter the brain from the systemic circulation where MDL 105,725 is formed from MDL 100,907.

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