Microdialysis Evaluation of Clozapine and N-Desmethylclozapine Pharmacokinetics in Rat Brain


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ABSTRACT:

A significant barrier to realization of the full potential of clozapine as a therapeutic agent in the treatment of schizophrenia is the substantial interpatient variability that exists along the therapeutic continuum of no response–efficacious response–adverse response. Genetic polymorphisms that manifest as highly variable pharmacodynamic and pharmacokinetic measures are its expected causes. To support investigations that seek to understand these causes, the plasma and central nervous system pharmacokinetics of clozapine were determined in rats, the latter using microdialysis sampling. Results obtained with clozapine and N-desmethylclozapine, a pharmacologically active human metabolite that was administered to a separate group of animals, support a conclusion of net carrier-mediated efflux of both compounds across the blood-brain barrier. These results are supported by the replication of published findings regarding the passive transport and net efflux transport of two model compounds, escitalopram and risperidone, respectively. The results obtained with clozapine and N-desmethylclozapine are considered a first step in the development of preclinical pharmacokinetic-pharmacodynamic models that will support deeper mechanistic studies of clozapine in vivo pharmacology, as well as the development of translational models that augment pharmacogenetic investigations that seek to improve the safety and efficacy of clozapine therapeutic intervention in the treatment of schizophrenia.

Introduction

Schizophrenia is a severe neuropsychiatric disorder characterized by a high degree of morbidity and mortality (Mathers et al., 2006). Over the past 50 years, pharmacotherapy has been an essential component in the management of this disease. Of the several drugs available, clozapine is widely considered the most efficacious (Horacek et al., 2006); however, its use in therapy is limited because of concerns about its safety (Spina et al., 2000). In particular, seizures, heightened risk of mortality in dementia-related psychosis, prolactin elevation, and weight gain are attributed to centrally mediated pharmacology and are consistent with classic dose-exposure-response causality.

The generally accepted aim of antipsychotic drug treatment is to achieve a therapeutic response quickly, in the early stages of symptom manifestation, and then to maintain this response. Unfortunately, in the case of clozapine, use of systemic drug levels to achieve these therapeutic aims while avoiding the adverse effects has met with limited success. This is due in large part to the substantial variability that exists between systemic exposure and clozapine’s centrally mediated effects (Spina et al., 2000). Over the past several years, this unpredictable exposure-response relationship has provided compelling justification for research to understand its pharmacokinetic (PK) and pharmacodynamic (PD) causes (Kane and Correll, 2010). The promise of such research is to develop individualized treatment approaches that are evidence-based, with pharmacogenetic evidence being a principal component.

Given the multiplicity of central nervous system (CNS) receptors that clozapine binds to and that are thought to contribute to its effects (Horacek et al., 2006), realization of the goal of individualized therapeutic regimens for clozapine has and will continue to prove challenging. Superimposed on this PD hurdle, genetic differences in clozapine disposition, including its metabolism by CYP1A2 and CYP3A4 (Mauri et al., 2007), create PK variability. Given the important role the blood-brain barrier (BBB) plays in limiting drug access to the brain through active efflux transport, genetic polymorphisms associated with such transport may also contribute to this PK variability. Although there is evidence of P-glycoprotein (Pgp) involvement in clozapine absorption across the BBB (Doran et al., 2005), relevancy of this transporter in vivo and the potential for other transporters, such as breast cancer resistance protein (BCRP), to influence clozapine BBB transport has not been thoroughly evaluated.

To support research that probes more deeply into the PD and PK manifestations of genetic polymorphisms that cause the substantial interpatient variability that exists between clozapine systemic exposure and clinical response, knowledge of clozapine concentrations in the extracellular fluid (ECF) of the brain would be useful. Awareness

ABBRVIATIONS: PK, pharmacokinetic(s); PD, pharmacodynamic(s); CNS, central nervous system; BBB, blood-brain barrier; Pgp, P-glycoprotein; BCRP, breast cancer resistance protein; ECF, extracellular fluid; MS/MS, tandem mass spectrometry; AUC_{0-\infty} area under the concentration-time curve from zero to infinity; KO, knockout; MDR, multidrug resistance.
of these concentrations in the biophase that is in intimate contact with CNS receptors and that is dependent on possible carrier-mediated BBB transport mechanism(s) would support investigations to determine the in vivo relevance of hypothesized PD and PK causes. Knowledge of ECF concentrations could be compared directly with in vitro-derived measures of clozapine-binding potency to all relevant receptors, both known and hypothesized. In this regard, we propose the use of quantitative microdialysis to measure ECF concentrations of clozapine in rats. With simultaneous measurement of plasma concentrations, development of a PK model that quantitatively relates systemic exposure to relevant CNS exposure would ensue. In addition, comparison of unbound clozapine concentrations in plasma with those in brain ECF would provide information regarding the potential involvement of active efflux transport of clozapine across the BBB. Use of microdialysis to fulfill these two objectives has been demonstrated for several CNS drugs (de Lange et al., 2005). In accord with these objectives, we describe herein an initial PK model that is expected to serve as a substrate to develop PK-PD models of clozapine action in well established rat models of antipsychotic drug action. In addition, application of PK scaling principles to predict human ECF concentrations from plasma exposure could also be explored. This second approach has shown promise for other CNS drugs (Kielbasa and Stratford, 2012).

Because N-desmethyloclozapine is an important active metabolite of clozapine in humans, we also determined its systemic and ECF PK in rats. Because this metabolite is relatively minor in rats, N-desmethyloclozapine was administered to a separate cohort of animals to characterize its PK. Finally, we also determined the systemic and CNS PK of escitalopram and risperidone in rats. Work with these two drugs provided context to our clozapine and N-desmethyloclozapine results with respect to potential involvement of active efflux transport across the BBB, with escitalopram serving as a model drug that exhibits predominantly passive transport (Bundgaard et al., 2007a) and risperidone serving as a model drug in which Pgp-mediated efflux occurs (Doran et al., 2005).

Materials and Methods

Drugs and Chemicals. The four compounds were purchased from Sigma-Aldrich (St. Louis, MO) and were used as received. Formulations for administration were prepared on the day of an experiment. Chemicals used in the preparation of microdialysis perfusion buffer and solvents used for high-performance liquid chromatography-tandem mass spectrometry (MS/MS) analysis were of reagent grade.

Animal Preparation. For the clozapine and N-desmethyloclozapine experiments, male Wistar rats weighing between 300 and 400 g were purchased from Harlan (Zei, The Netherlands). For escitalopram and risperidone experiments, male Wistar rats weighing between 280 and 350 g were used and also purchased from Harlan. Rats were individually housed in plastic cages and received food and water ad libitum. Experiments were performed in accordance with the declarations of Helsinki and were approved by the Animal Care Committee of the Department of Mathematics and Natural Science, University of Groningen.

Surgery for implantation of microdialysis guide cannula and venous catheters was conducted under isoflurane anesthesia (2% with 400 ml/min N2O and 400 ml/min O2). A guide cannula was inserted into the medial prefrontal cortex to achieve the following probe tip coordinates: anteroposterior, +3.3 mm from bregma; mediolateral, −0.8 mm; and dorsoventral, 5.0 mm from dura. Catheters (10-mm silicone tubing) for blood sample collection were inserted into the isolated right jugular vein and exteriorized through an incision at the top of the head. Animals were allowed at least 2 days to recover from surgery. MetaQuant probes [cellulose membrane, 4 mm (escitalopram and risperidone), 6 mm (clozapine and N-desmethyloclozapine); BrainLink, The Netherlands] were inserted 24 h before an experiment.

Drug-Binding Determination. Unbound plasma (f_u,p) and unbound brain (f_u,b) fractions for the four compounds were determined using a 96-well equilibrium dialysis apparatus (HTD Dialysis, Gales Ferry, CT) using a method detailed previously (Kalvass and Maurer, 2002; Kielbasa et al., 2009).

Drug Administration and Sample Collection. On the day of an experiment, rats were connected with flexible PEEK tubing to a CMA 102 microdialysis pump (CMA Microdialysis, Solna, Sweden). Microdialysis probes were perfused with 0.2% (w/v) bovine serum albumin dissolved in a filtered Ringer’s buffer containing 147 mM NaCl, 3.0 mM KCl, 1.2 mM CaCl2, and 1.2 mM MgCl2, at a flow rate of 0.1 μl/min (CMA 142 pump). The same buffer, but without albumin, was perfused through the dilution inlet of the probe at a flow rate of 0.8 μl/min. Under these conditions, compound recovery from probes was >98%, as determined from in vitro recovery experiments. After initiating flow, probes were allowed to stabilize for 1 h before compound administration. A single dose of each of the four compounds was administered by the subcutaneous route. There were four to five animals per compound. Clozapine and N-desmethyloclozapine were dosed at 10 mg/kg, and escitalopram and risperidone were dosed at 1.6 and 3 mg/kg, respectively. Per fusates from the microdialysis probes were collected every 30 min, starting 1 h before administration and continuing for 270 min (risperidone), 360 min (escitalopram), or 480 min (clozapine and N-desmethyloclozapine). Dialysate samples were stored at −80°C until the time of analysis. Blood samples (250 μl) were collected at 0, 15, 30, 60, 120, 180, 240, 300, and 360 (escitalopram only) min after escitalopram and risperidone administration and at 0, 15, 30, 60, 90, 120, 240, 360, and 480 min after clozapine and N-desmethyloclozapine administration. Blood samples were collected into microtubes containing 5 μl of heparinized (500 IE/ml) saline and were immediately centrifuged at 14,000 rpm for 10 min under refrigerated conditions to recover plasma. Plasma samples were stored at −80°C until the time of analysis.

Sample Analysis. Concentrations of compounds were measured in dialysate and plasma samples using high-performance liquid chromatography with MS/MS detection. The system consisted of an automated sample injector (Shimadzu SIL10, 20, or 30; Shimadzu, Kyoto, Japan), reverse-phase column, 150 × 2 mm, 5 μm (Phenomenex, Torrance, CA), and an API 4000 MS/MS with Turbo-Ion Spray interface (Applied Biosystems, The Netherlands) operating in the positive-ion mode with multiple reaction monitoring. Standard concentrations in dialysate ranged from 0.05 to 50.0 nM. In plasma, standard concentrations ranged from 1.0 to 20,000 nM for clozapine and N-desmethyloclozapine, from 4.0 to 20,000 nM for escitalopram, and from 20.0 to 20,000 nM for risperidone.

Pharmacokinetic Analysis. A PK modeling approach with distribution between plasma and brain ECF was used to describe the PK of the four compounds. The model shown in Fig. 1 was fit simultaneously to the unbound and plasma concentrations in rats using non-linear least-squares regression analysis (Phoenix WinNonlin 6.2; Pharsight, Mountain View, CA). Measured plasma concentrations were converted to undissociated concentrations by multiplying by the fraction unbound in plasma in .

The ECF equilibration half-life, t_1/2_Kp,u, was derived from the reciprocal of the unbound brain fraction, f_u,b, obtained from determinations made in brain homogenates (Fridén et al., 2007) and was fixed during the modeling procedure (Tunblad et al., 2004). The time course of ECF-to-plasma concentration ratio (K_p,u) was used to estimate the unbound brain (ECF) equilibrium rate constant, k_eq, and the steady-state ECF-to-plasma ratio, K_p,u,ss, according to the following equation:

The ECF equilibration half-life, t_1/2, was calculated from k_eq according to the following equation:

This analysis approach has been used previously to model the time course of whole brain-to-plasma ratios of several opiate drugs (Kalvass et al., 2007).

Results

Subcutaneous administration of a 1.6 mg/kg dose of escitalopram resulted in an average area under the concentration-time curve from
Plasma, unbound

risperidone or a 10 mg/kg dose of either clozapine or approximately 10% of clozapine AUC
findings in rats (Olsen et al., 2008), systemic exposure averaged only plasma concentrations are also shown. Consistent with previous
summarized in Fig. 2; also shown are measured brain ECF concen-
terences in brain ECF. Unbound plasma concentration time courses are similar for the four compounds, being within a 2.5-fold range (Table 1). Also shown in Table 1 are corresponding compound es-
porations in brain ECF. Unbound plasma concentration time courses are summarized in Fig. 2; also shown are measured brain ECF concentra-
tinations. In the case of clozapine administration, N-desmethylcloza-
pine plasma concentrations are also shown. Consistent with previous
findings in rats (Olsen et al., 2008), systemic exposure averaged only approximately 10% of clozapine AUC (31,165 versus 323,476 nM min). There was no detectable N-desmethylclozapine in the ECF after this dose of clozapine (lower quantitation limit = 0.05 nM).

Plasma and ECF PK parameter estimates derived from simultaneous
ous fitting of unbound plasma and ECF concentrations in individual animals to the model specified in Fig. 1 are summarized in Table 2. A
one-compartment model with first-order absorption was used to de-
scribe the plasma concentration time course data for clozapine, N-desmethylclozapine, and risperidone. Consistent with previous studies (Bundgaard et al., 2007a), escitalopram systemic exposure, sub-
sequent to first-order absorption, was best described using a two-
compartment approach. Precision (% CV) of the various parameter
estsimates in each animal was typically ~<25% across the four com-
ounds. Figure 3 summarizes model-predicted concentrations versus observed concentrations. For the four compounds, these data were close to and randomized across the line of unity, thus indicating an acceptable fit to the data. Relative to escitalopram, uptake clearance (Cl\text{in}) into the brain of the other compounds ranged from 8 (N-
desmethylclozapine) to 35% (clozapine). Conversely, efflux clearance (Cl\text{out}) from the brain was greater for these three compounds versus escitalopram, ranging from 1.7- (risperidone) to 2.7-fold (clozapine).

Table 3 summarizes various measures of the extent of ECF exposure relative to unbound plasma exposure for the four compounds. For escitalopram, the ratio of Cl\text{in}/Cl\text{out} of 1.24 ± 0.309 (mean ± S.D.) agrees with the previously reported finding of 0.80 (Bundgaard et al., 2007) and supports an interpretation of no net carrier-mediated uptake or efflux transport across the rat BBB. For each of the four compounds, this model-derived measure of BBB transport was in good agreement with the noncompartmental-derived (AUC ratio) and the steady-state ECF-to-plasma ratio (K\text{ss}) derived from this ratio versus time. The time course of K\text{p,e} for the four compounds is summarized in Fig. 4. Compared with escitalopram, these various measures for risperidone, which according to Pgp mouse knockout (KO) studies (Doran et al., 2005) is considered an ABCB1 (Pgp) substrate, were below unity and statistically lower (p < 0.01). These results are consistent with in vivo functional presence of carrier-mediated risperidone efflux across the BBB. Similar to risperidone, the three measures of BBB transport obtained for clozapine and N-desmethylclozapine were below unity and statistically lower than escitalopram (p < 0.01). Therefore, at the plasma exposures obtained in this study, operation of carrier-mediated efflux across the BBB is implicated for clozapine and its principal human pharmacologically active metabolite.

Discussion

Our goals in this work were to measure biophase exposure of clozapine and N-desmethylclozapine in the rat using brain microdialysis and to develop a PK model that describes the relationship between this pharmacologically relevant CNS exposure and plasma exposure. Although there is one report (Liu et al., 2009) of measured N-desmethylclozapine in rat brain ECF derived from microdialysis measures, there are no reported studies regarding clozapine ECF exposure using this technique. We believe the stated goals are important because they represent the initial step in the development of a rat-to-human translatable PK-FD model that quantifies the relationship between brain biophase concentrations and those in plasma. Given that clozapine binds to a multiplicity of receptors (Horacek et al., 2006), such a model has the potential to be more robust in advancing our understanding of preclinical and clinical antipsychotic

<table>
<thead>
<tr>
<th>Drug</th>
<th>f\text{ep}</th>
<th>AUC\text{p,0-\infty}</th>
<th>C\text{max,p,u}</th>
<th>T\text{max,p,u}</th>
<th>AUC\text{ECF}</th>
<th>C\text{ss,ECF}</th>
<th>T\text{max,ECF}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>nh min</td>
<td>nM</td>
<td>min</td>
<td>nM</td>
<td>nh min</td>
<td>nM</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>50</td>
<td>13,888 (12)</td>
<td>131 (27)</td>
<td>26 (29)</td>
<td>11815 (10)</td>
<td>62 (23)</td>
<td>120 (35)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>61 (4)</td>
<td>19,732 (49)</td>
<td>77 (41)</td>
<td>60 (41)</td>
<td>2659 (49)</td>
<td>6 (33)</td>
<td>240 (18)</td>
</tr>
<tr>
<td>N-desmethylclozapine</td>
<td>11 (8)</td>
<td>32,296 (34)</td>
<td>90 (77)</td>
<td>63 (157)</td>
<td>805 (55)</td>
<td>2 (64)</td>
<td>278 (47)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>16 (7)</td>
<td>24,022 (18)</td>
<td>181 (32)</td>
<td>53 (29)</td>
<td>3543 (17)</td>
<td>20 (23)</td>
<td>75 (23)</td>
</tr>
</tbody>
</table>

* Escitalopram f\text{ep} estimate is from Bundgaard et al., 2007a.
drug action compared with a receptor occupancy-based PK-PD model that is based on one or two receptors.

Quantitative microdialysis has been used to evaluate escitalopram CNS PK in rats after intravenous administration (Bundgaard et al., 2007a,b). On the basis of model-independent (AUC) and -dependent (\(C_{\text{in}}, C_{\text{out}}\)) analyses in these studies, there was no evidence of carrier-mediated uptake or efflux of escitalopram across the BBB, and it was concluded that transport of this drug occurs predominantly by a passive mechanism. In these studies, quantitative microdialysis was achieved using dynamic-no-net flux and/or retrodialysis. Herein, we describe results obtained with MetaQuant microdialysis probes (BrainLink). These probes rely on the principle of ultraslow flow microdialysis (\(\sim 200 \text{ nl/min}\)) to achieve quantitative recovery of analyte (Cremers et al., 2009) while maintaining temporal resolution typical of standard microdialysis probes. On the basis of the ECF exposures attained with this approach, and achieving plasma exposures similar to those reported by Bundgaard et al. (2007a), we arrive at the same conclusion: namely, that there is no evidence that escitalopram transport

![Graph](https://example.com/graph1.png)

**FIG. 2.** Time course of unbound plasma (triangles) and brain ECF (squares) concentrations in individual animals for escitalopram, clozapine, N-desmethylclozapine, and risperidone after single subcutaneous administration of 1.5, 10, 10, and 3 mg/kg, respectively. Corresponding average (mean ± S.D., \(n = 4\) rats per compound) concentrations are shown as solid lines (plasma) or dashed lines (ECF). Average N-desmethylclozapine unbound plasma concentrations after clozapine administration are also shown (dotted line).

<table>
<thead>
<tr>
<th>Drug</th>
<th>(V_c)</th>
<th>(Cl)</th>
<th>(k_{a})</th>
<th>(V_p)</th>
<th>(Q_{d})</th>
<th>(V_{b,u})</th>
<th>(Cl_{in})</th>
<th>(Cl_{out})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram</td>
<td>4.1 (34)</td>
<td>277 (32)</td>
<td>0.02 (43)</td>
<td>17 (39)</td>
<td>117 (58)</td>
<td>18</td>
<td>0.19 (39)</td>
<td>0.16 (52)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>275 (12)</td>
<td>2006 (49)</td>
<td>0.04 (97)</td>
<td>70</td>
<td>0.07 (50)</td>
<td>0.44 (38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-desmethylclozapine</td>
<td>607 (83)</td>
<td>1597 (83)</td>
<td>0.50 (68)</td>
<td>82</td>
<td>0.02 (59)</td>
<td>0.38 (68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>21 (50)</td>
<td>307 (21)</td>
<td>0.03 (53)</td>
<td>10</td>
<td>0.05 (25)</td>
<td>0.32 (12)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* \(V_{b,u}\) estimates \(= f_{u,b} V_{b,u}\) and were fixed during the modeling. For escitalopram, \(f_{u,b}\) was 3.1% and taken from Bundgaard et al. (2007a). For clozapine, N-desmethylclozapine, and risperidone, \(f_{u,b}\) estimates were 0.8 (2), 0.7 (10), and 6.5% (8), respectively [mean (% CV)].
across the BBB occurs by active carrier-mediated transport processes. These similar findings provide additional verification with respect to the use of MetaQuant technology for quantitative microdialysis, which is a more facile approach, requiring fewer experiments and animals than either the dynamic-no-net flux or the retrodialysis approach.

As with escitalopram, risperidone was selected as a model drug to support and add context to interpretations made regarding the clozapine and N-desmethylclozapine results. Specifically, risperidone was selected as a drug in which net efflux across the BBB was expected. There are several reports based on Mdr1a KO models demonstrating that Pgp reduces risperidone uptake into the brains of both mice (Wang et al., 2004; Doran et al., 2005; Summerfield et al., 2006) and rats (Bundgaard et al., 2012). Using plasma and brain homogenate free fraction analysis, efflux asymmetry was observed in mice (Mau-
rer et al., 2005) and rats (Watson et al., 2009). In a study involving direct measurement by microdialysis of risperidone in brain ECF of rats and comparison to unbound plasma concentrations after intravenous infusion over 6 h, Liu et al. (2009) reported a risperidone steady-state ECF-to-plasma, ratio of 0.53. Because this value was within 3-fold of a ratio of 1, the authors concluded that there was no clear evidence in vivo of risperidone efflux across the BBB. On the basis of the three measures of extent of brain ECF exposure relative to unbound plasma concentration (AUC, model-derived bidirectional clearance ratio and $K_{pu,ss}$) summarized in Table 3, our results support a conclusion of net efflux of risperidone across the BBB and are consistent with a Pgp-mediated mechanism. Our study and the Liu et al. (2009) study both used rats but different routes of administration (subcutaneous versus intravenous infusion), so it is not possible to directly compare plasma exposures and comment regarding the potential for saturation of efflux. Both studies were at a single dose level. In view of the several studies that have been performed on this drug in relation to its BBB transport and Pgp role in such transport, a focused study with a full plasma and ECF time course at different doses would seem worthwhile and represent a comprehensive in vivo analysis of the potential saturability of Pgp-mediated efflux at this site.

The ability to discriminate between a drug with predominantly passive BBB transport (escitalopram) and one with net efflux-medi-

### Table 3

<table>
<thead>
<tr>
<th>Drug</th>
<th>AUC_{ECF}/AUC_{pu,u}</th>
<th>Cl_{pu}/Cl_{tot}</th>
<th>$K_{pu,ss}$</th>
<th>$k_{eq}$</th>
<th>$t_{1/2,eq}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram</td>
<td>0.86 (13)</td>
<td>1.24 (25)</td>
<td>1.06 (42)</td>
<td>0.015 (42)</td>
<td>194 (23)</td>
</tr>
<tr>
<td>Clozapine*</td>
<td>0.15 (37)</td>
<td>0.16 (36)</td>
<td>0.13 (33)</td>
<td>0.004 (26)</td>
<td>165 (48)</td>
</tr>
<tr>
<td>N-desmethylclozapine*</td>
<td>0.03 (74)</td>
<td>0.05 (60)</td>
<td>0.04 (85)</td>
<td>0.006 (87)</td>
<td>165 (48)</td>
</tr>
<tr>
<td>Risperidone*</td>
<td>0.15 (9)</td>
<td>0.14 (16)</td>
<td>0.21 (39)</td>
<td>0.006 (72)</td>
<td>165 (63)</td>
</tr>
</tbody>
</table>

* AUC and Cl ratios, and $K_{pu,ss}$ significantly different (p < 0.01) vs. corresponding escitalopram values according to one-way analysis of variance followed by the Tukey t test for multiple comparisons.

**Fig. 4.** Brain ECF to unbound plasma concentration ratio ($K_{pu,u}$) versus time data in individual rats (diamonds). Corresponding average (mean ± S.D.; n = 4 rats per compound) concentrations are shown as solid lines. Data are derived from the concentration data presented in Fig. 1.
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ated transport (risperidone) augments our ability to interpret results obtained with clozapine and N-desmethylclozapine. As with risperi-
done, the various measures of brain distribution we observed support a conclusion for clozapine and its metabolite that net efflux occurs across the rat BBB (Table 3). The results for clozapine are somewhat

...mine this rate (Liu et al., 2005). The 3-fold difference is believed...


