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Brain Extracellular Levels of the Putative Antipsychotic CI-1007 and Its Effects on Striatal and Nucleus Accumbens Dopamine Overflow in the Awake Rat

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Abstract

The compound CI-1007 (*R*-(+)-1,2,3,6-tetrahydro-4-phenyl-1[(3-phenyl-3-cyclohexen-1-yl)methyl]pyridine maleate) has been identified as a partial dopamine agonist and putative antipsychotic in in-vitro and in-vivo neurochemical, neurophysiological and behavioural tests.

By use of microdialysis in conjunction with high-performance liquid chromatography (HPLC) with electrochemical detection, the effects of the drug on brain dopamine release, previously observed in anaesthetized animals, were shown to occur in awake animals also. Detection of peripherally administered CI-1007 in the brain, i.e. evidence of the drug's ability to penetrate the blood–brain barrier, was achieved by use of in-vivo brain microdialysis in awake, freely moving rats and capillary HPLC in combination with tandem mass spectrometry (HPLC/MS/MS). Intravenous administration of CI-1007 ($40\,mg\,kg^{-1}$) significantly inhibits dopamine release in the nucleus accumbens, a region associated with dopamine hyperactivity in schizophrenia, while having a non-significant impact on the striatal dopamine neurotransmission which is critical to regular motor function.

The differential neurochemical profile of the drug indicates its potential usefulness in treating positive disease symptoms and implies that its extrapyramidal side effects are lower than those of typical antipsychotics.

Dopaminergic hyperactivity in brain mesolimbic areas such as the nucleus accumbens is thought to underlie positive symptoms of schizophrenia (Weinberger et al 1992). Modulating brain dopamine neuronal activity has been a useful approach in developing therapy for the disease and potent dopamine antagonists have proved efficacious in treating positive symptoms (Seeman 1980, 1987; Carlsson 1988). However, therapies focusing solely on dopamine antagonism produce motor disorders (extrapyramidal side effects and tardive dyskinesia) associated with postsynaptic dopamine-receptor blockade in dopaminergic terminal regions such as the striatum (Seeman 1987; Vinick & Heym 1987) and are ineffective in a significant patient subpopulation. This underscores the need for alternative strategies such as reducing dopaminergic activity with partial agonists which exert dopamine-agonistic properties at presynaptic dopamine autoreceptors but have little postsynaptic dopamine D_2 receptor affinity. Presynaptic dopamine autoreceptor activation inhibits dopamine neuronal firing, synthesis and release (Aghajanian & Bunney 1977; Roth 1984; White & Wang 1984).

In the search for a compound with optimum intrinsic activity, i.e. with an optimum balance between actions at pre- and postsynaptic dopamine sites, a series of cyclohexenes with partial dopamine agonistic properties have been synthesized at Parke-Davis (Wright et al 1994). The compound CI-1007 (PD 143188-6614; *R*-(+)-1,2,3,6-tetrahydro-4-phenyl-1[(3-phenyl-3-cyclohexen-1-yl) methyl]-pyridine maleate) (Figure 1) was identified as a partial dopamine agonist and putative antipsychotic in in-vitro and in-vivo neurochemical, neurophysiological and behavioural tests (Meltzer et al 1995; Pugsley et al 1995). An important criterion in evaluating a compound as a centrally acting drug is to show that it penetrates the blood–brain barrier. A sensitive and specific assay for the drug in-vivo is therefore required.

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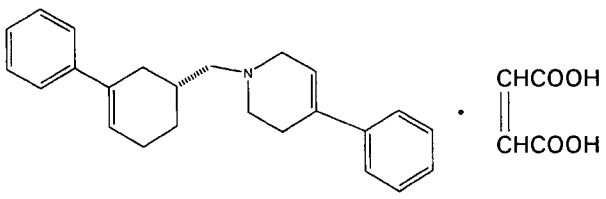

Figure 1. Structure of CI-1007 (PD 143188-6614; *R*-(+)-1,2,3,6-tetrahydro-4-phenyl-1[(3-phenyl-3-cyclohexen-1-yl)-methyl]-pyridine maleate).

Microdialysis enables sampling of brain extracellular fluid for measurement of endogenous neurotransmitters and exogenous substances (Robinson & Justice 1991). Mass spectrometry (MS) has emerged as a highly sensitive and specific tool for pharmaceutical studies (Niessen & van der Greef 1992). In particular, the introduction of ionization sources such as electrospray (Meng et al 1988; Fenn et al 1989) and atmospheric-pressure chemical ionization (Shahin 1967; French et al 1985) has enabled the facile combination of liquid chromatography with mass spectrometry such that after chromatographic separation substances can be measured with great sensitivity and specificity in biological matrices such as brain extracellular fluid by MS detection, particularly MS/MS. The product ion MS/MS spectrum is obtained by allowing only the analyte ion of interest (parent ion), selected by mass-to-charge ratio (m/z), to undergo collisional dissociation in the presence of an inert gas, a process which produces products of the parent ion. Thus, a product ion MS/MS detection paradigm can be devised to record only those product ions originating from ions that have the same m/z as the desired parent ion. The net result is an analytical method that affords selective detection of product ions that are unique signatures of the analyte of interest and high sensitivity as a result of reduction of chemical noise.

We have used in-vivo brain microdialysis in awake, freely moving rats and capillary HPLC/MS/MS to demonstrate the presence of peripherally administered CI-1007 in the brain, as evidence of the ability of the drug to penetrate the blood–brain barrier. Using microdialysis in conjunction with HPLC-electrochemical detection, we have also demonstrated that the effects of the drug on brain dopamine release, previously observed in anaesthetized animals, occur in awake animals also.

Materials and Methods

Chemicals

CI-1007 maleate salt was synthesized at Parke-Davis. Dopamine, bovine serum albumin (BSA) and 2-hydroxypropyl-β-cyclodextrin were obtained from Sigma (St Louis, MO) and were used without further purification. Analytical-reagent grade salts were used to prepare artificial cerebrospinal fluid. Eighteen megohm cm water and HPLC-grade acetonitrile (CH_3CN) were used to prepare all solutions. Protein-sequencing-grade trifluoroacetic acid (TFA) was obtained from Applied Biosystems (Foster City, CA).

CI-1007 assay

Gradient chromatography. Separations were performed by use of a Michrom Bioresources (Auburn, CA) Magic HPLC system and a 0·3 mm i.d. × 50 mm Monitor C_{18} analytical column. Reversed-phase gradient HPLC with 30-min run-time and a nominal 10 μL min^{-1} flow rate employed a precolumn split and a balance column (Monitor 1 mm i.d. × 50 mm C_{18}). The mobile phase was prepared from two solvent mixtures: A, composition H_2O–CH_3CN–acetic acid-TFA, 98 : 2 : 0·1 : 0·02, and B, H_2O–CH_3CN–acetic acid–TFA, 10 : 90 : 0·09 : 0·02. The amount of solvent B in the mobile phase was increased from 5 to 95% in 20 min. The column was left to re-equilibrate for 15 min between analyses. UV data was collected for each sample to monitor HPLC-gradient delivery and solvent-flow reproducibility. All samples were injected manually.

Mass spectrometry. Fused silica tubing (40 μm i.d.) was used to deliver the HPLC effluent, via a Valco Instruments (Houston, TX) grounded divert valve (omitting the manufacturer-supplied grounded union) to the electrospray interface of a Finnigan LCQ quadrupole ion-trap mass spectrometer (Thermo Separations, San Jose, CA). During the first 5 min after each HPLC injection the valve was used to divert the unretained artificial cerebrospinal fluid salts and thereafter to direct effluent to the spectrometer. CI-1007 MS/MS detection was optimized by infusing a 1 ng μL^{-1} solution of the drug in a 30 : 70 (v/v) mixture of HPLC solvents A and B at 10 μL min^{-1} into the spectrometer, via a Harvard syringe pump. The electrospray voltage, tube lens and capillary voltages, heated capillary temperature, sheath and auxiliary gas pressures and collision energy were optimized. The electrospray voltage and heated capillary-inlet temperature were maintained at 3·4 kV and 200°C, respectively. Nitrogen was used as sheath gas.

Dopamine assay

Brain microdialysates were assayed for their dopamine content by isocratic HPLC with electrochemical detection, using a BAS LC-4B amperometric detector equipped with a narrow-bore

3·2 mm i.d. × 100 mm (ODS-3, 3 μm) C_{18} reversed-phase analytical column (Bioanalytical Systems, IN). The mobile phase composition was 9·5 g L^{-1} chloroacetic acid, 45 mg L^{-1} 1-octanesulphonic acid, 38 mg L^{-1} Na_2EDTA, and 20 mL L^{-1} tetrahydrofuran (THF); pH 2·8. The flow rate was 0·6 mL min^{-1}. The glassy-carbon working electrode potential was maintained at +0·75 V relative to an Ag/AgCl reference electrode.

Microdialysis

Animal preparation. Male Sprague-Dawley rats (Harlan), 225–325 g, were anaesthetized with halothane, placed on a heating pad maintained at 37°C and CMA 12 microdialysis probes (CMA Microdialysis, MA) with 4 mm or 2 mm active lengths were unilaterally implanted in the striatum or nucleus accumbens, respectively. To minimize tissue damage, probes were lowered at a rate that required approximately 15 min for implantation. The stereotaxic coordinates (Paxinos & Watson 1982) were: 2·7 mm lateral to midline, 0·5 mm anterior and 7 mm below dura for the striatum; and 1·6 mm lateral, 1·6 mm anterior and 8 mm below dura for the nucleus accumbens. Two skull screws were implanted and the probes were fixed in place with dental cement. The animals were placed in clear plexiglass chambers, attached through a tether to a liquid swivel and allowed to recover from surgery overnight, during which time the probe was perfused with artificial cerebrospinal fluid at 0·5 μL min^{-1}. Dialysate collection was initiated the following day. CI-1007 levels were measured in the striatum only, whereas the effects of the drug on dopamine release were studied in both striatum and nucleus accumbens. After completion of each experiment, animals were killed by urethane overdose and the brains were removed and placed in formalin. Probe placement was verified by visually inspecting tissue slices.

Artificial cerebrospinal fluid. For CI-1007 assays the composition of the perfusion solution was: KCl, 2·4 mM; NaCl, 137 mM; $CaCl_2$, 1·2 mM; $MgCl_2$, 1·2 mM and 0·001% (w/v) BSA, pH 7·0. BSA was included to minimize non-specific adsorption of the drug by the walls of the microdialysis tubing. The composition of the perfusion medium for dopamine assay was the same except that BSA was excluded. Artificial cerebrospinal fluid was filtered through 0·45-μm filters before use. For CI-1007 measurement, artificial cerebrospinal fluid was perfused at 0·3 μL min^{-1} and samples were collected at 30-min intervals in 0·5-mL Eppendorf vials, frozen at −70°C and analysed within a week of collection. Samples for dopamine analysis were collected at 30-min intervals at a perfusion rate of 2 μL min^{-1} and analysed immediately after collection.

Probe recovery

CI-1007 recovery was determined in-vitro by placing a probe perfused with artificial cerebrospinal fluid in a vial containing a drug solution of known concentration (C_{ext}). Recovery (%) was calculated by use of the formula $C_{perfusate}/C_{ext} \times 100$, where $C_{perfusate}$ is the concentration of drug in the solution collected from the probe. CI-1007 values reported herein are uncorrected dialysate levels.

Drug preparation and dosing

CI-1007 maleate salt was dissolved, with sonication, in 10% (w/v) 2-hydroxypropyl-β-cyclodextrin in 0·9% saline vehicle. The pH of the drug solution was adjusted to 5·0 with 1 M NaOH. Intraperitoneal bolus administration was performed with volumes corresponding to a 40 mg kg^{-1} dose (free base). Animals in the dopamine experimental group received a vehicle injection 90 min before drug administration.

Data analysis

The CI-1007 content of microdialysate samples was estimated by comparison with the response obtained from 5 pg standard. Basal dopamine values were calculated as the mean of values in three samples taken before drug treatment. Results are presented as the percentage of the basal value. Post-treatment mean dopamine levels were compared with the mean basal dopamine level at time 0 by means of Student's two-sample *t*-test. A Bonferroni adjustment was used to adjust for multiplicity of statistical testing.

Results

CI-1007 assay

Probe recovery. HPLC with ultraviolet (UV) detection, on the basis of triplicate measurements from three individual probes, indicated that mean probe recovery of CI-1007 was 31%. For three successive 20-min samples collected, variation in recovery for each probe was within 15% of the mean percent recovery.

Gradient chromatography. The Monitor C18 column afforded efficient gradient separation of CI-1007 with a mobile phase containing a TFA concentration (0·02%) one-fifth of those typically used. Small (< 2 min) day-to-day variations in retention time were sometimes observed.

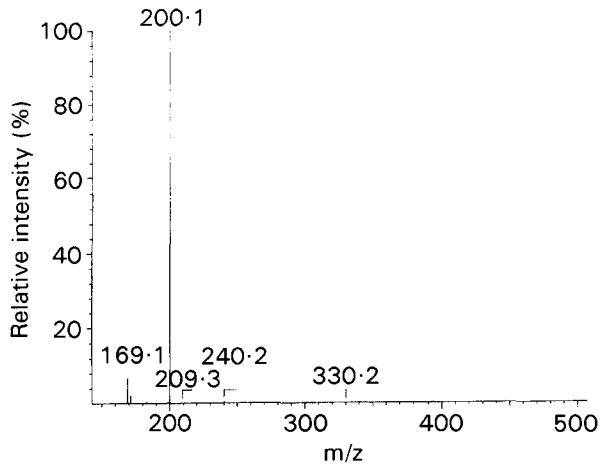

Figure 2. Product ion spectrum of the CI-1007 $[M+H]^+$ ion.

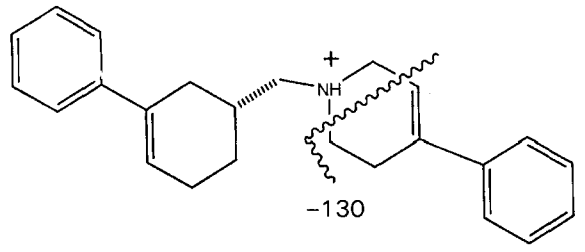

Figure 3. Proposed structure of MS/MS product ion (m/z 200) resulting from ion-collision-activated dissociation of the CI-1007 $[M+H]^+$ ion.

Mass spectrometry. The electrospray mass spectrum of CI-1007 contained primarily a single peak at m/z 330·3, corresponding to the singly protonated free base $[M+H]^+$. Collisional dissociation of the $[M+H]^+$ ion in the presence of He gas yielded a product ion (m/z 200) which accounted for 90–95% of the total ion current (TIC) under optimized conditions. The product ion spectrum of m/z 330, $[M+H]^+$, and the proposed fragmentation, initiated around the basic nitrogen of the piperidine group, are shown in Figures 2 and 3, respectively. The transition 330·3 → 200 was monitored by selected-reaction monitoring for detection of the drug in microdialysate. The total ion-current trace obtained from an artificial cerebrospinal fluid blank is illustrated in Figure 4A. The MS detector response for standards was linear between 0·5 pg and 5 pg on-column. A 0·5 pg (on-column) CI-1007 standard in 5 μL artificial cerebrospinal fluid typically yielded a S/N ratio of 10 : 1 in the mass chromatogram (Figure 4B). This amount is equivalent to 0·1 pg μL^{-1} and was regarded as the limit of quantitation (LOQ). A typical response from 5 pg standard is shown in Figure 4D.

Analysis of microdialysates. CI-1007 (free base; 40 mg kg^{-1}) was administered intraperitoneally to three animals. Figure 4C depicts the response obtained from a sample (animal B, 150 min post-dose). The striatal dialysate drug concentrations measured at different times for the group are shown

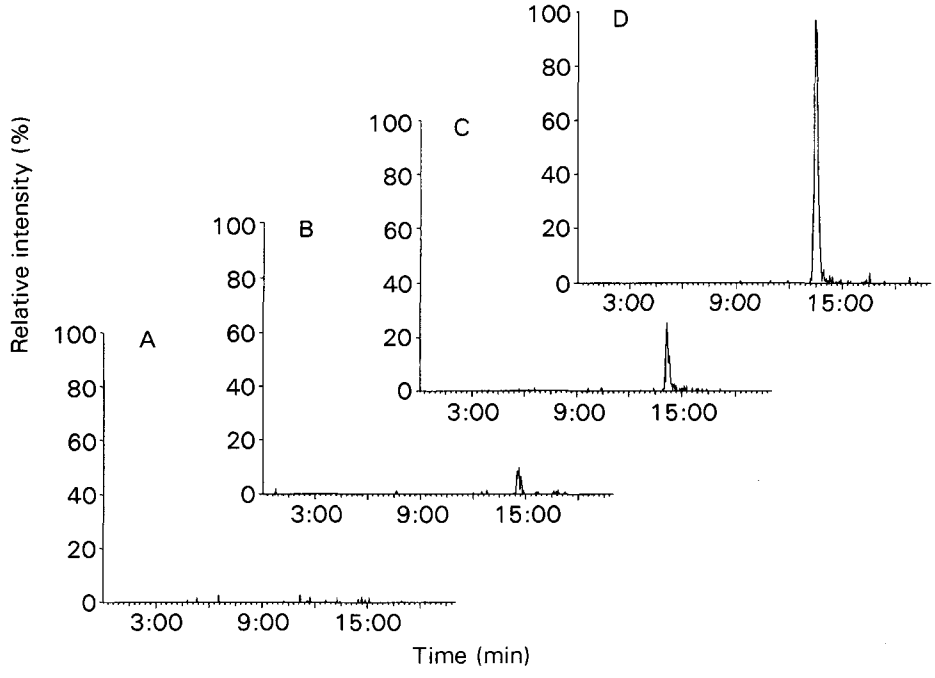

Figure 4. HPLC-MS-MS chromatograms. A. Artificial cerebrospinal fluid blank; B. 0·5 pg CI-1007 standard in 5 μL artificial cerebrospinal fluid; C. sample from animal B, 150 min after administration of drug; D. 5 pg CI-1007 standard in 5 μL artificial cerebrospinal fluid.

Table 1. Time dependence of the concentration of CI-1007 in the striatal dialysate in three awake rats after intraperitoneal bolus administration of 40 mg kg^{-1} of the drug.

Animal	Concentration (pg μL^{-1}) after time (min)					
	30	60	90	120	150	180
A	< 0·1	ND*	< 0·1	ND	< 0·1	ND
B	ND	0·2	0·1	< 0·1	0·3	< 0·1
C	ND	ND	0·1	< 0·1	ND	ND

ND, not detected.

in Table 1. Samples which gave responses below the LOQ (S/N < 10 : 1) but in which CI-1007 was clearly detected (S/N > 3 : 1) are simply reported as containing concentrations of CI-1007 < 0·1 pg μL^{-1}. In the animals tested the maximum amounts of drug in a 9-μL sample did not exceed 3 pg.

Dopamine assay

Levels of dopamine measured in dialysates were consistent with those generally observed (1 fmol μL^{-1} for striatum and 0·3–0·5 fmol μL^{-1} for nucleus accumbens). Results are presented as percent change from basal values (Figure 5).

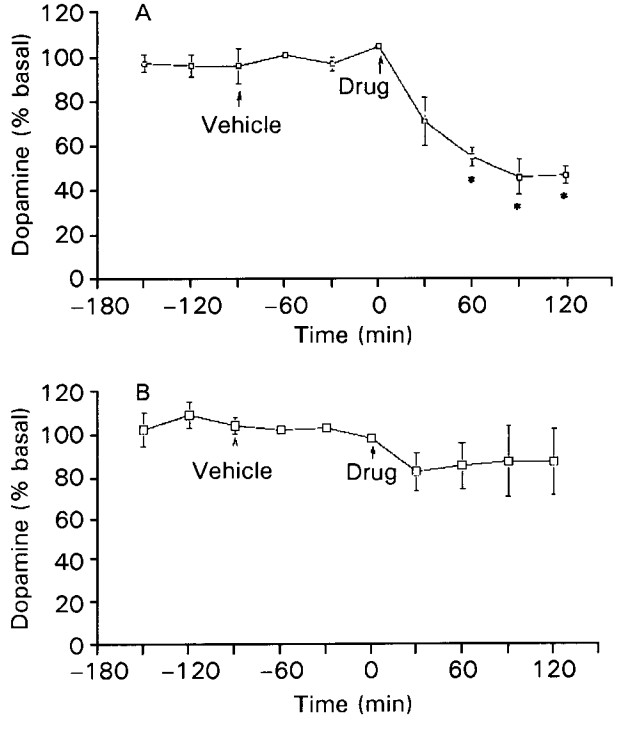

Figure 5. Effects of intraperitoneal bolus administration of 40 mg kg^{-1} CI-1007 on dopamine release in A. the nucleus accumbens (n = 3) and B. the striatum (n = 5) of awake rats. * $P < 0·01$, significantly different from basal dopamine level with vehicle.

Administration of vehicle elicited less than 10% alteration of basal dopamine in both regions when monitored for 30 min after administration. Subsequent intraperitoneal treatment with 40 mg kg^{-1} CI-1007 led to a decrease in basal dialysate dopamine in the nucleus accumbens of approximately 45%. The *t*-test indicated a statistically significant difference between basal dopamine level and levels 60, 90 and 120 min after treatment ($P = 0·0003$, $P = 0·0020$ and $P = 0·0002$, respectively). Dopamine release in the striatum was attenuated by approximately 15% only. The *t*-test indicated that in the striatum there were no statistically significant differences between basal dopamine level and post-treatment levels. Maximum inhibition of dopamine release in the nucleus accumbens occurred 60–90 min after drug treatment whereas attenuation of striatal dopamine efflux was maximum 30–60 min after treatment.

Discussion

CI-1007 assay

Inclusion of the ion pairing agent TFA in the mobile phase at the concentrations typically used, e.g. 0·1% (v/v), results in significant attenuation of the electrospray MS signal. Reducing the TFA content increases MS response, but usually adversely affects chromatographic performance. Highly efficient end-capping of residual silanol groups on the Monitor C_{18} column enables its use with a mobile phase containing 0·02% TFA (Baldwin et al 1996). Development of a high-sensitivity assay for CI-1007 was partly achieved by using a lower concentration of TFA in the mobile phase and an analytical column compatible with reduced TFA concentrations. Minimum post-column transfer volume (ca. 1·6 μL) was achieved by grounding the divert valve, eliminating the manufacturer-supplied grounding union and using a small (40 μm) i.d. transfer line. This resulted in a minimum of chromatographic band broadening before MS detection. Minor day-to-day variations in HPLC retention time were probably a result of slight changes in the pre-column split ratio. The split ratio was not monitored daily because the selectivity of the MS-MS detection scheme meant that small changes in retention time were not problematic.

Detection of CI-1007 in striatal dialysate

Use of a highly sensitive and specific HPLC/MS/MS assay in this study has enabled monitoring of the penetration of the drug through the blood–brain barrier and suggests that its biochemical and behavioural effects might be mediated via central sites of action. The data indicate

inter-animal variability in the length of time during which the drug was detected. Animals were dosed 18–24 h after probe implantation to allow adequate time for the blood–brain barrier to recover from probe-related damage. The temporal profile, reflecting delayed appearance of the drug in the dialysate, suggests that the drug penetrated a functional blood–brain barrier. Dialysate drug levels did not exceed 0·5 pg μL^{-1}. Probe recoveries for CI-1007 determined in-vitro were adequate to suggest that the low dialysate drug levels measured did not arise from loss in in-vivo efficiency. The lower dialysis flow rate employed in these experiments (0·3 $\mu L\,min^{-1}$) was used to maximize the concentration of drug in the dialysate and to minimize the sample volume for capillary HPLC analysis. The low concentrations of CI-1007 observed in the dialysate are consistent with data indicating that the drug is highly lipophilic, is of moderate bioavailability and is tightly bound to plasma proteins (Feng et al 1993, 1994). The molecular weight cut-off of the dialysis membrane used in the CI-1007 assay was 20 kD, which precluded entry of extracellular fluid protein into the probe, thus excluding protein-bound CI-1007. Another source of drug sequestration might be intracellular accumulation; proof of this will require comparison of concentrations in extracellular fluid and brain tissue.

Dopamine measurement

Presynaptic dopamine autoreceptors residing on dopaminergic nerve terminals modulate dopamine synthesis and release (Clark et al 1985a, b). Dopamine partial agonists are selective for presynaptic autoreceptors compared with postsynaptic D_2 receptors, presumably because of low intrinsic agonist activity or a large receptor reserve on presynaptic areas compared with postsynaptic sites (Carlsson 1983; Meller et al 1987). A partial agonist selective for the dopamine autoreceptor might be expected to inhibit dopaminergic neurotransmission to a lesser extent than agents that are potent antagonists at postsynaptic dopamine sites. Reduced extrapyramidal side effects might therefore be expected with dopamine partial agonists. Pharmacological and behavioural studies using CI-1007 in urethane-anaesthetized rats (Meltzer et al 1995; Pugsley et al 1995) have indicated that the compound is a dopamine partial agonist and a putative antipsychotic.

Because basal dopamine levels varied among animals, data are presented as percentage changes from basal values. Intraperitoneal treatment with 40 mg kg^{-1} CI-1007 significantly inhibited dopamine efflux in the nucleus accumbens, while having little impact in the striatum of awake, freely moving rats. Maximum inhibition of dopamine release in the nucleus accumbens occurred 60–90 min after drug treatment, whereas striatal dopamine efflux was maximally attenuated 30–60 min after treatment. The results corroborate data obtained in a previous study (Pugsley et al 1995) on the effect of 20 mg kg^{-1} intraperitoneal CI-1007 on dopamine release in the nucleus accumbens and striatum of urethane-anaesthetized rats—greater inhibition of dopamine release in the nucleus accumbens than in the striatum. The drug's differential neurochemical profile reflects its projected therapeutic benefits. The robust effect on nucleus accumbens dopamine suggests that CI-1007 might ameliorate positive symptoms of schizophrenia by inhibiting dopaminergic hyperactivity in this brain region. Concomitantly, the weak effect in the striatum indicates that the drug has a minimum impact on dopamine activity necessary for dopamine-dependent, striatum-mediated motor function and suggests reduced extrapyramidal side effects.

Conclusions

This study demonstrates the ability of the putative antipsychotic CI-1007 to cross the blood–brain barrier and the utility of relatively inexpensive, commercially available bench-top MS-MS instruments for the detection of ultra-trace amounts of the drug in biological matrices. When acutely administered to awake rats CI-1007 significantly inhibits dopamine release in the nucleus accumbens, a region associated with dopamine hyperactivity in schizophrenia, while making a minimum impact on striatal dopamine neurotransmission, which is critical to regular motor function. The differential neurochemical profile of the drug indicates its potential usefulness in treating positive disease symptoms and suggests lower extrapyramidal side effects than for conventional antipsychotics.

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