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BRIEF REPORT

The in Vitro Actions of Loxapine on Dopaminergic and Serotonergic Receptors. Time to Consider Atypical Classification of This Antipsychotic Drug?

Florian Ferreri, Dominique Drapier, Emmanuelle Baloche, Mehemed Ouzid, Luc Zimmer, Pierre-Michel Llorca

Sorbonne Universités, UPMC Paris, France; Department of Psychiatry, Hospital Saint-Antoine, Paris, France (Dr Ferreri); Université de Rennes 1, Rennes, France (Dr Drapier); Department of Psychiatry, Rennes University Hospital, Rennes, France (Dr Drapier); EISAI SAS, La Défense, Paris, France (Ms Baloche and Dr Ouzid); Université Claude Bernard Lyon1, CNRS, INSERM, Lyon, France (Dr Zimmer); CERMEP-Imaging Platform, Hospices Civils de Lyon, Lyon, France (Dr Zimmer); CMP B, CHU Clermont-Ferrand, Clermont-Ferrand, France (Dr Llorca).

Correspondence: Florian Ferreri, MD, PhD, UPMC Paris Univ-06, Paris, France; Department of Psychiatry, Hôpital Saint-Antoine, 184 rue du Faubourg Saint-Antoine 75012 Paris, France (florian.ferreri@upmc.fr, florian.ferreri@aphp.fr).

Abstract

Background: The denomination of typical antipsychotic for loxapine has poor relation to current knowledge of the molecule’s relevant modes of action.

Materials and Methods: Competition binding experiments were performed on expressed human recombinant receptors in CHO cells and HEK-293 cells for D₁ to D₅, 5-HT₁A, 5-HT₂A, 5-HT₂C, 5-HT₄, 5-HT₆, and 5-HT₇. In vitro autoradiographies using [¹¹C]-Raclopride [¹⁸F]-Altanserin [¹⁸F]-MPPF [¹¹C]-SB207145, and [¹⁸F]-2FNQ1P were measured in brain tissue of a male primate followed by addition of increasing doses of loxapine succinate.

Results: In cell cultures, the measured Kb confirmed high affinity of loxapine for the D₂; intermediate affinity for the D₁, D₄, 5-HT₂A, 5-HT₂C, 5-HT₄, 5-HT₆, and 5-HT₇. In brain tissue, PET autoradiographies showed a radiopharmaceutical displacement at low concentrations of loxapine on D₂ and 5-HT₂A receptors.

Conclusion: This preclinical study reveals that loxapine receptorial spectrum is close to an “atypical” profile (D₂/5HT₂A ratio, 1.14). Loxapine is rightly classified as a DS-RAn agent in the Neuroscience Based Nomenclature classification.

Keywords: loxapine, binding, PET radiopharmaceutical, dopamine receptor, serotonin receptor

Introduction

Loxapine is considered as a well-known first-generation antipsychotic. In terms of chemistry, loxapine is a dibenzoazepine molecule, with a tricyclic structure chemically close to clozapine. This molecule, initially released in the mid-1970s, is available for oral, i.m., and, more recently, oral inhalation use (Keating, 2013).

Loxapine has been used for the treatment of schizophrenia and agitated adult since the 1970s. The recent approval by regulatory agencies in the United States and European Union of loxapine inhalation powder in the acute treatment of agitated adult patients with schizophrenia or bipolar disorder renews interest in this molecule (Keating, 2013; Popovic et al., 2015).
Currently, prescribers interested in this drug have little pharmacological information at their disposal (Popovic et al., 2015). A systematic literature search about the pharmacological properties of loxapine leads to a small number of publications, mainly with old data not recently updated and hard to reach online. Particularly, the receptor binding spectrum of loxapine is only documented by public data available in the PDSD Ki Database (National Institute of Mental Health).

Among these sparse data, it appears that loxapine is usually classified as a “typical” antipsychotic (or first-generation antipsychotic). Its antipsychotic efficacy is proposed to be mainly mediated through antagonism of postsynaptic dopamine D_{2} receptors. This status, shared by the majority of first-generation neuroleptics, explains that loxapine is essentially prescribed as a second or third choice antipsychotic.

Several authors have proposed that loxapine has “atypical” characteristics (Glazer, 1999; Chakrabarti et al., 2007). The atypicality of an antipsychotic is mainly but not only defined by its receptor binding profile, especially the high-affinity antagonism of serotonin 5-HT_{2A} in complement to dopamine D_{2} receptor antagonism, leading to a high 5-HT/D_{2} occupancy ratio (Meltzer et al., 1989). However, no recent experimental data have been released to confirm this new classification of loxapine.

As a consequence, the in vitro receptor binding profile of typical and atypical antipsychotic drugs is frequently without any mention to loxapine (Kusumi et al., 2015). This poor literature is a real drawback for a comprehensive and evidence-based medicine loxapine prescription, pharmaceutical processing, and monitoring of utilization.

Neuropsychopharmacology is a major tool to manage side effects, switches, and molecule association (e.g., introduction or cessation of theloxapine administration). The knowledge of the neuropsychopharmacological profile of loxapine makes us all the more interested in the question, since the classical classification is currently in evolution. Some of the major international neuropsychopharmacology associations (ECNP, ACNP, Asian CINP, and CINP) propose a modification of psychotropic classification. Its aim is to address a longstanding concern within the neuropsychopharmacological community and psychiatric communities that the nomenclature of current psychotropic drugs, including antipsychotics, does not properly reflect the underlying mechanism of action of these compounds (Zohar et al., 2015). The Neuroscience Based Nomenclature proposes a new template placing pharmacology rather than indication as the primary axe.

In this emerging and challenging context, the purpose of our study is to describe loxapine’s serotonin and dopamine receptor occupancy in vitro using various techniques. The first aim was to focus on dopamine and serotonin receptors, crucial in the antipsychotic effect, in a classical receptor binding strategy. The second aim was to transfer this receptor exploration toward in vitro positron emission tomography (PET) by using clinical radiopharmaceuticals in autoradiography performed with nonhuman primate brain tissues.

**Materials and Methods**

**Receptor Binding Protocols**

In a first step, the respective affinities (Kb) of loxapine succinate (provided by EIUSA) were determined toward dopamine receptors (D_{1}, D_{2}, D_{3}, D_{4}, and D_{5}) and serotonin receptors (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_{2B}, 5-HT_{3A}, 5-HT_{4}, and 5-HT_{6}) by Cerep, an in vitro pharmacology company (http://www.cerep.fr). Competition binding experiments were performed on expressed human recombinant receptors in CHO and HEK-293 cells (vs SCH 23390, butaclamol, (+)butaclamol, clozapine, SCH2390, WAY100635, ketanserin, SB206553, GR113808, methiothepin, for D_{1}, D_{2}, D_{3}, D_{4}, D_{5}, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_{3A}, 5-HT_{4}, 5-HT_{5}, and 5-HT_{6}, receptors, respectively). Each experiment was performed in duplicate at 5 different concentrations. IC_{50} values (concentration eliciting half-maximal inhibition of the control specific agonist response) were determined by nonlinear regression analysis of the concentration–response curves generated with mean replicate values using Hill equation curve fitting. Analyses used the commercial SigmaPlot 11.0 software (Systat Software Inc.). The Kb values were calculated using the modified Cheng Prusoff equation (see https://www.eurofins.com/biopharma-services/ for supplementary experimental details).

**PET Radiopharmaceutical Syntheses and Quality Controls**

On the days of autoradiography experiments, PET radiopharmaceuticals were produced and handled in the CERMEP-Imaging Platform. [11C]-Raclopride and [18F]-SB207145 radiopharmaceuticals were obtained after [11C]-methylation of their respective chemical precursors in an automated synthesizer for [18F]-PET radiopharmaceuticals (Scansys) according to methods previously published (Lassoun et al, 2003; Madsen et al, 2011). [3F]-altanserin (5-HT_{2A} receptors), [3F]-MPPF (5-HT_{1A} receptors), and [3F]-2F-NQ1P (5-HT receptors) radiopharmaceuticals were radiolabeled by [3F]-nucleophilic substitution of their respective chemical precursors in an automated synthesizer for [3F]-fluorinated PET radiopharmaceuticals (Ora) according to previously described radiochemical pathways (Haugbol et al, 2007; Becker et al, 2014, 2015). Their chemical and radiochemical purities, as measured by HPLC, were >98%. The specific activity at time of autoradiography was >37 GBq/mmol (1 Ci/mmol) for all PET radiopharmaceuticals.

**Autoradiography Protocols and Image Analyses**

A nonhuman male primate ( cynomolgus monkey; 6 kg body weight) was used for this study in accordance with European guidelines for care of laboratory animals (2010/63/ EU) and with the ethics committee of the University of Lyon (Université Claude Bernard Lyon 1). After killing by an overdose isoflurane inhalation, the primate brain was carefully removed and immediately frozen in 2-methylbutane cooled with dry ice (~29°C). Briefly, horizontal sections (30 µm thick)
cut across the hippocampus and the striatal region were carried out using a −20°C-cryostat (Microm-Microtech), thaw-mounted on glass slides, and allowed to air dry before storage at −80°C until used.

On the days of radiosynthesis, the slides were allowed to reach ambient temperature and then incubated for 20 minutes in Tris-phosphate-buffered saline buffer (138 mM NaCl, 2.7 mM KCl, pH adjusted to 7.6) containing 37 kBq/mL (1 µCi/mL) of the radiopharmaceutical, e.g., [11C]-Raclopride, [18F]-Altanserin, [18F]-MPPF, [11C]-SB207145, and [18F]-2FNQ1P.

For competition experiments, the slides were placed in the same buffer supplemented with loxapine succinate (1 nM, 10 nM, 50 nM, 100 nM, and 1 µM). After incubation, the slides were dipped in cold buffer (4°C) for 90 seconds, then dried and juxtaposed to a phosphor imaging plate for 60 minutes (BAS-1800 II, Fujifilm). Regions of interest (cortical regions, caudate, putamen, and hippocampus) were drawn manually using Multigauge software (Fujifilm). The results were expressed in arbitrary units.

**Results**

**Receptor Binding Protocols**

The measured Kb demonstrated high affinity of loxapine succinate for the D2 receptor and 5-HT2A receptor with a value <2 nM (Figure 1). Loxapine succinate presented intermediate affinity for the D1, D4, D5, and 5-HT2C receptors, with a Kb value between 12 and 29 nM. In these experimental conditions, loxapine succinate presented total lack of affinity toward D3, 5-HT1A, 5-HT5, and 5-HT7 receptors (Kb > 1 µM).

| Dopamine Receptors | Loxapine Affinity (Kb) |
|--------------------|------------------------|
| D1                 | 29 nM                  |
| D2                 | 2.4 nM                 |
| D3                 | NS                     |
| D4                 | 12 nM                  |
| D5                 | 28 nM                  |

| Serotonin Receptors | Loxapine Affinity (Kb) |
|--------------------|------------------------|
| 5-HT1A             | NS                     |
| 5-HT2A             | 2.1 nM                 |
| 5-HT2C             | 22 nM                  |
| 5-HT4              | NS                     |
| 5-HT6              | NS                     |
| 5-HT7              | NS                     |

**PET Autoradiography**

The autoradiography distribution of receptor radiotracers varied across the striatal regions for [11C]-Raclopride, [11C]-SB207145, and [18F]-2FNQ1P, according to the known distribution of D2, 5-HT2A, and 5-HT7 receptors, respectively. The distribution of [18F]-Altanserin was cortical as known for 5-HT2A receptor location. Finally, the binding of [18F]MPPF was correlated with the known distribution of 5-HT1A receptors, mainly located in hippocampus (Figure 2).

These PET autoradiographies allow the measurement of radiopharmaceutical displacements/competition at different concentrations of loxapine succinate. A competition occurred at low concentrations of loxapine on D2 receptors (~50% of [11C]-Raclopride displacement at 10 nM, ~80% at 50 nM, and ~90% at 100 nM of loxapine, respectively). In a similar manner, the displacement of [18F]-altanserin (5-HT2A receptors) was significant at 10, 50, and 100 nM of loxapine (~30%). Radiopharmaceutical displacements were observed at higher concentrations of loxapine on 5-HT1A receptors (~40% at 100 nM and ~90% of [18F] MPPF at 1 µM of loxapine) and 5-HT7 receptors (~20% of [18F] 2FNQ1P at 50 and 100 nM of loxapine, respectively). No effect was measured on 5-HT4 receptors ([11C] SB207145).

**Discussion**

The aim of the first part of this study was to have an updated overview of the receptor binding spectrum of loxapine focused on the classical receptors involved in the antipsychotic effects (e.g., D2, 5-HT2A receptors…) on other receptors involved in complementary psychopharmacological effects (e.g., 5-HT1A, 5-HT7, 5-HT6, receptors…) or receptors responsible of possible
side effects (H₁, M₁ receptors...). A total of 20 targets have been explored in vitro in cellular cultures. The aim of the second part of this study was more translational with the use of PET radiopharmaceuticals in nonhuman brain tissues focused on targets having their own radioligand (D₂, 5-HT₂A, 5-HT₁A, 5-HT₄, and 5-HT₆ receptors), with competition experiments at increasing doses of loxapine.

The main results of our study can be summarized as:

1. Loxapine succinate has in vitro a high affinity for the D₂ receptor and 5-HT₂A receptor with a 5-HT₂A/D₂ ratio superior to 1;
2. These in vitro results are confirmed in nonhuman primates with PET radiopharmaceuticals, by a high displacement potency loxapine for D₂ receptors, and 5-HT₂A receptors at low concentrations;
3. The in vivo PET study revealed that loxapine has possibly a significant affinity for other serotoninergic receptors (5-HT₁A and 5-HT₆), which can be related to the clinical profile this compound.

All antipsychotics have actions at dopamine D₂ receptors. “Atypical” ones, with a more loosely binding than dopamine and a dissociation constant higher than dopamine to these receptors (Seeman, 2002), may have a different action compared with “typical” on it. In addition, they block SHT-2 receptors (Stahl, 2003), and the ratio of blockade of compounds of this class goes from 0.07 for clozapine to >100 for fluphenazine (Horacek et al., 2006). In clinical practice, this combination of 5-HT with D₂ blockade is related to the lower induction of extrapyramidal side effects but also to the effect observed on negative symptoms (Stahl, 2003).

With a 5-HT₂A/D₂ ratio >1, loxapine is shown to be close to an “atypical” profile, since its 5-HT₂A occupancy is higher than its D₂ occupancy. This study also demonstrates that loxapine succinate presented intermediate affinity for the D₁, D₄, D₅, and 5-HT₂C receptors, a nonsignificant affinity toward D₃, 5-HT₁A, 5-HT₄, 5-HT₆, and 5-HT₇ receptors. These results are in accordance with earlier preclinical studies describing its pharmacological action involving strong dopamine D₂ receptor antagonism in addition to blocking activity at D₁ and serotonin-2 (5-HT₂) receptors as well (Singh et al., 1996). These binding results must be discussed.

A high level of 5-HT₂ occupancy is not a sufficient condition for “atypicity” (in its clinical aspect). If atypical antipsychotic action is predicated on a combination of 5-HT₂ and D₂ effects, then it requires >80% 5-HT₂ occupancy in conjunction with <80% D₂ occupancy. Threshold D₂ occupancy for EPS seems higher (84%) for olanzapine than others. Antipsychotic drugs with intrinsic anticholinergic activity may be associated with an upper threshold for EPS (Uchida et al.).

Figure 2: Dopaminergic and serotonergic PET radiopharmaceutical in vitro distributions in macaque brain. Monkey cerebral sections were processed for in vitro autoradiography with [¹¹C]-Raclopride, [¹⁸F]-Altanserin, [¹⁸F]-MPPF, [¹¹C]-SB207145 and [¹⁸F]-2FNQ1P under baseline condition and in presence of increasing concentrations of loxapine. * indicate a significant decrease of the radiopharmaceutical binding (p<0.05).
As shown in a recent review publication (Popovic et al., 2015), loxapine at 10 to 100 mg/d was found to be equipotent at blocking D₂ and 5-HT₂ receptors.

Another contribution of our study is the use of PET radiopharmaceuticals. Our study is the first to provide PET autoradiographies on nonhuman primate brain tissue for loxapine. Nonhuman primate tissue is close to the neuroanatomy and the receptorology found in human subjects (Phillips et al., 2014). With respect to D₂ activity, a competition occurred at low concentrations of loxapine on D₂ receptors. In a similar manner, the displacement of [¹⁸F]-altanserin (5-HT₂A receptors) was significant and constant (~30%) from 10 nM to 100 nM. Regarding the 5-HT₂A receptors, they are blocked at low doses like most atypical antipsychotic drugs (Seeman, 1981). Loxapine’s superior affinity for 5-HT₂ (vs D₂) observed in vitro was not found in our PET study. A previous PET study in schizophrenic patients found comparable results with a D₂ receptor occupancy from 43% to 90% and a 5-HT₂ receptor occupancy from 27% to near saturation (Kapur et al., 1997). These discrepancies between in vivo and in vitro results can be explained by the higher affinity of the 7-hydroxyloxapine, a loxapine metabolite, for D₂ receptors.

Another factor to be considered in the interpretation of the results is linked to the dosage of the molecule. According to PET studies in patients, antipsychotic threshold occupancy of D₂ for antipsychotic action is about 65% for both “typical” and “atypical” antipsychotic drugs, regardless of whether 5-HT₂A receptors are blocked or not, and extrapyramidal side effects occurs at about 80% of D₂ receptor occupancy (Seeman, 2002). These in vivo data cannot be directly reproduced in our in vitro experimental conditions, according to the fact we used the same clinical radiopharmaceuticals. In other words, the possible significant affinity of loxapine for 5-HT₂A and 5-HT₂ receptors we observed in primate brain tissue, and which was not measured in cellular cultures, has to be confirmed in vivo using the same radiotracers. Doses used have an important impact on receptor spectrum; selection of an antidepressant must take into account these binding profiles to ensure the antipsychotic effect at low doses and avoid the known adverse events (Correll et al., 2010). According to the literature and our results, at low doses (<100 mg/d), loxapine can be considered as “atypical” (5-HT₂A/D₂ ratio). At higher doses, the loxapine profile is more typical (strong D₂ blocking). The potential antidepressant effect (5-HT₁A/5-HT₆ antagonism) of loxapine needs additional clinical investigations.

Several methodological drawbacks and experimental limitations must be highlighted. Firstly, we must be careful before extrapolating the results of the binding study according to the fact that recombinant human cells (CHO, HEK-293, and GH4) overexpress the receptors in nonphysiological conditions. For example, binding results obtained for 5-HT₂A and 5-HT₂ receptors in the cellular model were not in accordance with those obtained in the nonhuman primate brain tissue. The concentrations of ligand should also be considered, because the specific connections of a given ligand is saturable as it corresponds to a definite number of receptors. Additionally, the activities of the metabolites are not taken into account. Secondly and despite its preclinical uses, the PET imaging has well known limitations. All brain receptors of interest cannot be explored in vivo because of the currently limited number of PET radiopharmaceuticals (Zimmer and Luxen, 2012). If PET in vitro autoradiography in nonhuman primates is a potent translational method, it does not reproduce the in vivo production of metabolites (e.g., amoxapine, a loxapine’s metabolite with a significant 5-HT₂ receptor affinity). Finally, extrapolation of in vitro loxapine concentrations to in vivo brain concentrations is difficult. If competition studies with PET autoradiography can provide important data about loxapine affinity and binding properties toward receptors, only in vivo PET studies can measure the relation between the dose, the real receptor occupancy, and the clinical effect, all in a longitudinal manner (Zimmer and Luxen, 2012).

Perspectives

The practical application of pharmacological knowledge in clinical practice has become an important issue of optimizing patients’ treatment. Individualized treatment approaches need to consider current symptoms, comorbid conditions, as well as pharmacological aspects of medications (Correll et al., 2010). Our experimental approach focuses only on the pharmacological characteristics (and not on clinical issues resulting from the therapeutic effects). This approach is current since the recent new classification of psychotropic drugs focused on the brain targets (and not on the psychiatric indications).

To date, first line treatment for psychotic disorders is second-generation (“atypical”) antipsychotics. For decades, in clinical practice, loxapine has been a commonly used antipsychotic. However, its pharmacological mode of action was not yet been clearly established. Is loxapine a “typical” or an “atypical” antipsychotic? Historically classified as a typical antipsychotic, loxapine differs from these first-generation antipsychotics. Loxapine’s receptor binding is equipotent in blocking 5-HT₂ and D₂ receptors. Thus, in the Neuroscience Based Nomenclature classification (Zohar et al., 2015), according to its receptor affinity profiles, loxapine can be classified as a DS-RAn (Receptor antagonist D₂, 5-HT₂) with chlorpromazine, iloperidone, lurasidone, olanzapine, paliperidone, sertindole, thioridazine, ziprasidone, and zotepine. Our study will help, providing a better understanding of loxapine’s pharmacological domains of action. Taking into account our results, further studies of loxapine active metabolites (8-hydroxyloxapine and 7-hydroxyloxapine) and a dose-ranging study will be conducted.

Conclusion

This article is an update of the dopamine-serotonin receptor binding characteristics of loxapine, a molecule that has a particular place between “typical” and “atypical” antipsychotics. This approach is needed and is in accordance with the newly proposed psychotropic drug reclassification (Zohar et al., 2015).

At low doses, loxapine is shown to be in vitro close to an atypical profile, since its 5-HT₂A binding occupancy is higher than its D₂ binding (high 5-HT₂A/D₂ ratio). Our study also emphasizes the role of other targets (D₆, D₄ receptors). Widely used in acute situations at high dose, there is need for further PET studies exploring long-term prescriptions.

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Statement of Interest

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