Comparison of the Effects of Clozapine, Risperidone, and Olanzapine on Ketamine-Induced Alterations in Regional Brain Metabolism

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ABSTRACT
The ability of subanesthetic doses of N-methyl-D-aspartate (NMDA) antagonists to induce positive, negative, and cognitive schizophrenia-like symptoms suggests that reduced NMDA receptor function may contribute to the pathophysiology of schizophrenia. An increasing body of evidence indicates that antipsychotic drugs, especially those with “atypical” properties, can antagonize the effects of NMDA antagonists in a variety of experimental paradigms. We demonstrated previously that clozapine, the prototype of atypical antipsychotics, but not haloperidol, the typical antipsychotic, blocked ketamine-induced alterations in brain metabolism. In this study, effects of clozapine were compared with two of the newer atypical antipsychotic drugs, risperidone and olanzapine, on ketamine-induced alterations in regional [14C]2-deoxyglucose (2-DG) uptake. A subanesthetic dose of ketamine (25 mg/kg) induced robust increases in 2-DG uptake in limbic cortical regions, hippocampal formation, nucleus accumbens, and basolateral amygdala. Pretreatment of rats with risperidone (0.3 mg/kg) before ketamine administration did not alter the effects of ketamine. These data suggest that novel pharmacological properties may contribute to the effects of clozapine in this model, in addition to the well characterized actions at D2 and 5HT2A receptors. In contrast to the results with risperidone, olanzapine blocked ketamine-induced increases in 2-DG uptake. However, a higher dose of olanzapine (10 mg/kg) was required to completely block the effects of ketamine than would be expected if D2 and 5HT2 receptor blocking properties of the drug were solely responsible for its action. The results suggest that the ketamine challenge 2-DG paradigm may be a useful model to identify antipsychotic drugs with atypical characteristics and to explore mechanisms of atypical antipsychotic action.

Discovery of the remarkable efficacy of clozapine for the treatment of schizophrenia fostered a new era of antipsychotic drug development and has encouraged new pathophysiological theories of schizophrenia (for review, see Kinon and Lieberman, 1996). Clozapine is effective in patients who are resistant to treatment with typical antipsychotics and has not induce the extrapyramidal side effects (EPS) characteristic of these agents (for review, see Bradford et al., 1998). The weak D2 receptor blocking properties of clozapine readily explain the virtual absence of EPS induced by the drug and also suggest a fundamentally different therapeutic mechanism of action in comparison with the typical antipsychotic agents (Kapur et al., 1999). Unfortunately, administration of clozapine is associated with other serious side effects in some patients, including agranulocytosis and seizures, that impose substantial limitations on its use.

Development of new antipsychotic drugs that have the beneficial properties of clozapine without inducing adverse side effects has been hampered due to insufficient understanding of the mechanisms of action of clozapine. Clozapine has weak antagonistic actions at D1 and D2 dopamine receptors and more potent antagonistic actions at 5HT2A, 5HT2C, 5HT6, 5HT7, α1- and α2-adrenergic, H1 histamine, and M1 muscarinic receptors (Kinon and Lieberman, 1996; Meltzer, 1996). In addition, clozapine has 5HT1A receptor agonistic properties (Rollema et al., 1997). Whether any of these actions of clozapine, alone or in combination, account for its therapeutic efficacy is uncertain.

The rationale for development of the newer antipsychotic drugs, such as risperidone and olanzapine, and their classification as atypical has been based predominantly on antagonistic properties at 5HT2A and D2 receptors. However, it may be prudent to consider additional mechanisms of antipsychotic drug action and strategies for drug discovery based on pathophysiological hypotheses of schizophrenia other

ABBREVIATIONS: EPS, extrapyramidal side effects; 2-DG, [14C]2-deoxyglucose; PPI, prepulse inhibition; NMDA, N-methyl-D-aspartate; PCP, phencyclidine.
than dopamine- and serotonin-based hypotheses. In this regard, the N-methyl-D-aspartate (NMDA) receptor hypofunction hypothesis of schizophrenia (Javitt and Zukin, 1991; Olney and Farber, 1995) may provide a novel theoretical framework for investigating mechanisms of action of antipsychotic drugs.

Subanesthetic doses of NMDA receptor antagonists, such as ketamine and phencyclidine (PCP), can induce a spectrum of behavioral responses in healthy human volunteers that resemble positive, negative, and cognitive schizophrenia-like symptoms (Krystal et al., 1994; Malhotra et al., 1996). Furthermore, ketamine can precipitate psychoses in schizophrenic patients (Lahti et al., 1995; Malhotra et al., 1997). The psychosis induced by NMDA antagonists is somewhat different from amphetamine-induced psychosis, the latter being associated predominantly with positive symptoms (Lieberman et al., 1987). The ability of subanesthetic doses of NMDA antagonists to induce a spectrum of schizophrenia-like symptoms in humans provides strong support for the NMDA hypofunction hypothesis of schizophrenia.

Subanesthetic doses of ketamine induce robust increases in regional \(^{14}\text{C}\)2-deoxyglucose (2-DG) uptake (Duncan et al., 1998a,b), presumably by disrupting neural circuits via disinhibitory actions. The striking alterations in brain metabolic activity patterns induced by subanesthetic doses of ketamine were almost identical with those induced by the selective NMDA antagonist, MK-801 (Duncan et al., 1999). These data indicate that the neuroanatomically selective effects of ketamine on 2-DG uptake result from reduced NMDA receptor function. In a previous study, we found that pretreatment of rats with clozapine, but not with haloperidol, blocked the brain metabolic activation induced by ketamine (Duncan et al., 1998b). Such data indicate that the paradigm of ketamine-induced brain metabolic activation may be useful for identifying drugs with atypical antipsychotic characteristics.

This study examined the effects of two antipsychotic drugs, risperidone and olanzapine, which are generally classified as atypical, on ketamine-induced alterations in 2-DG uptake. Risperidone was chosen for study for its potent antagonistic activity patterns induced by subanesthetic doses of ketamine and pharmacology with properties more closely resembling clozapine. Therefore, it was of interest to characterize the actions of olanzapine with regard to its effects on ketamine-induced alterations in brain metabolism.

**Materials and Methods**

**Animal Treatments.** A total of 94 male Sprague-Dawley rats (Harlan Laboratories, Haslett, MI) was used. The rats weighed 200 to 275 g, were housed under a 12-h light/dark cycle with lights on at 7:00 AM, and had continuous access to food and water. All procedures were in strict accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the University of North Carolina Institutional Animal Care Committee.

Jugular catheters were implanted under pentobarbital anesthesia and exteriorized at the base of the neck. After surgery, rats were housed singly for 3 to 5 days, and catheters were flushed daily with 0.9% saline to acclimate them to experimental procedures. Rats were transported from the animal quarters to the laboratory 4 to 6 h before initiation of the 2-DG experiment. Vehicle, risperidone (0.3 mg/kg, dissolved in cyclohextran, 22% v/v), olanzapine (5.0 or 10 mg/kg, dissolved in 0.9% saline containing 10 \(\mu\)l of 20% acetic acid/ml), or clozapine (5 mg/kg, same vehicle as olanzapine) were injected i.p. 30 min before i.p. injection of ketamine (25 mg/kg) or 0.9% saline. Thus, the different treatment conditions were: vehicle-vehicle, antipsychotic-vehicle, vehicle-ketamine, and antipsychotic-ketamine.

The doses chosen for the different drugs are based on previously published in vivo studies. Risperidone is a potent 5HT\(_2\) receptor antagonist in vivo. Reported ED\(_{50}\) values for risperidone to block behavioral effects of dopamine agonists are between 0.06 and 0.1 mg/kg (Janssen et al., 1988; Megens et al., 1994; Arnt, 1995). For blocking 5HT\(_{2A}\) mediated responses in vivo, ED\(_{50}\) values for risperidone are 0.02 to 0.03 mg/kg (Janssen et al., 1968; Megens et al., 1994; Zhang and Bymaster, 1999). Therefore, the dose of 0.3 mg/kg risperidone is a relatively high dose of the drug with respect to D\(_3\) and 5HT\(_2\) antagonism. Regarding olanzapine and clozapine, Corbett et al. (1995) and Bakshi and Geyer (1995) found that 5 to 10 mg/kg of these drugs blocked behavioral effects of NMDA antagonists, and work from our group demonstrated that clozapine, at a dose of 5 mg/kg, effectively blocked ketamine-induced alterations in 2-DG uptake (Duncan et al., 1998b).

**High Resolution Autoradiographic Analysis of 2-DG Uptake.** The high-resolution autoradiographic procedures for analysis of 2-DG uptake have been described in detail (Duncan et al., 1993, 1998a). Behavioral activation was evident within 2 min after ketamine injection in vehicle-pretreated rats. Therefore, the 2-DG (300 mC\(\mu\)mol, 0.4 \(\mu\)Ci/g b.w.; American Radiolabeled Chemicals, St. Louis, MO) was administered via the jugular catheter 2 min after i.p. injection of ketamine or saline. Rats were sacrificed by decapitation 5 min after the i.v. injection of 2-DG to ensure a constant behavioral state during the 2-DG uptake period. We have demonstrated that a 5-min survival period after i.v. injection of 2-DG is useful for the study of time-limited behavioral events (Duncan et al., 1993, 1998a,b). The data obtained using a 5-min survival time after injection of 2-DG represent an index of brain metabolic activity and reflect a composite of regional brain blood flow, transport of 2-DG into the brain, and phosphorylation of the metabolic indicator. Brains were frozen on an aluminum block cooled with liquid nitrogen and stored at \(-80^\circ\text{C}\) until sectioned. Kodak SR1 Industrex film (Rochester, NY) was cut into rectangular pieces approximately three-quarters of the length of microscope slides and glued to one end of the slides with silicone adhesive. Cryostat sections (10 \(\mu\)m) of the brains were thaw-mounted onto the slide-mounted film under safe-light conditions and stored in light-tight desiccator boxes at room temperature for exposure periods of 4 to 6 weeks. The autoradiograms produced by thaw-mounting sections onto the high-resolution film were used for photographic documentation of 2-DG uptake patterns. This method of producing autoradiograms allows a more refined neuroanatomical analysis in comparison with standard procedures because of the improved resolution obtained with the very small silver grain size in the SR1 Industrex film and the more intimate association between the brain sections and film emulsion produced by thaw-mounting sections directly onto the film. For quantitative analysis, other sections were mounted onto microscope slides and apposed to Kodak Industrial T film in X-ray cassettes, along with \(^{14}\text{C}\) microscale standards (Amersham Pharmacia Biotech, Piscataway, NJ) for 2 weeks.

**Autoradiograms of sections and \(^{14}\text{C}\) standards were digitized with a high-resolution transparency scanner (Saphir Ultra; Linotype-Hell, Happpauge, NY) and analyzed with NIH Image software. Seven brain regions were chosen for quantitative evaluation based on our previous investigation of the effects of ketamine on 2-DG uptake. Each of the seven brain regions was analyzed in six sections for each animal, and each treatment condition was analyzed by observers who were blind to the treatment conditions. The amount of radioactivity in each brain region for each rat was determined by reference to the \(^{14}\text{C}\) standards and subsequently expressed as a percentage of the control value for each experiment for statistical analysis.**
Statistics. PC-based SYSTAT software (version 6.0; SPSS, Chicago, IL) was used for statistical analysis. Data of 2-DG uptake were analyzed separately for each brain region. For each experiment, a set of planned comparisons were evaluated by ANOVA. The specific planned comparisons were chosen to assess whether the antipsychotic drugs alone altered 2-DG or whether they altered the effects of ketamine on 2-DG uptake. Bonferroni corrections were applied to each set of comparisons to correct for alpha inflation.

Results

Lack of Effect of Risperidone on Ketamine-Induced Alterations in 2-DG Uptake. Administration of a subanesthetic dose of ketamine increased 2-DG uptake in the medial prefrontal cortex, nucleus accumbens, cingulate cortex, anteroventral thalamic nucleus, basolateral nucleus of the amygdala, and stratum lacunosum-moleculare of the hippocampus (Figs. 1, 3, and 4). In the lateral frontal (parietal) cortex, no apparent change in 2-DG uptake was observed after ketamine (Fig. 1). Administration of risperidone (0.3 mg/kg) tended to reduce 2-DG in all regions, but the effects were small (10–20%) and not significantly different from the vehicle group in any region. Pretreatment of rats with risperidone before ketamine administration did not significantly alter the effects of the NMDA antagonist on 2-DG uptake in any region (Fig. 1).

Effects of Olanzapine and Clozapine on Ketamine-Induced Alterations in 2-DG Uptake. An initial experiment tested the effects of 5 mg/kg of olanzapine. No effect of 5 mg/kg olanzapine alone was observed on 2-DG uptake in any region (Fig. 2). At this dose, olanzapine significantly reduced the ketamine-induced increases in 2-DG uptake in the medial prefrontal cortex and basolateral nucleus of the amygdala (Fig. 2). Although there was a tendency for 5 mg/kg olanzapine to reduce ketamine-induced alterations in other brain regions, differences between the saline-ketamine and olanzapine-ketamine groups were not significant at the $P < .05$ level.

To determine whether a higher dose of olanzapine would block ketamine-induced brain metabolic activation more effectively, a dose of 10 mg/kg was tested. In addition, for comparison, effects of clozapine (5 mg/kg) were examined in the same experiments. Representative autoradiograms of brain sections are shown in Figs. 3 and 4, and quantitative data are shown in Fig. 5. Both 10 mg/kg olanzapine and 5 mg/kg clozapine alone tended to reduce 2-DG uptake in most brain regions, but the reductions in uptake compared with saline-treated rats were small and not statistically significant for any region. Both olanzapine and clozapine blocked the effects of ketamine on 2-DG uptake in the medial prefrontal cortex, nucleus accumbens, anteroventral thalamic nucleus, basolateral nucleus of the amygdala, and stratum lacunosum-moleculare of the hippocampus (Figs. 3–5). Not only were the large ketamine-induced increases in 2-DG uptake blocked by olanzapine and clozapine, but the amount of 2-DG uptake observed in rats that received both drugs before ketamine tended to be lower than control values.

Discussion

Although clozapine is recognized as the prototypal atypical antipsychotic drug, there are no well defined criteria for characterizing newly developed antipsychotics as atypical. Meltzer et al. (1989) suggested defining an antipsychotic as atypical based on antagonistic actions at both D$_2$ and 5HT$_2$ receptors as well as clinical criteria of minimal induction of EPS at therapeutic doses. Kinon and Lieberman (1996) suggest defining an antipsychotic as atypical based on clinical efficacy and a low propensity to induce EPS with short-term treatment and no induction of tardive dyskinesia after long-term treatment. For rational development of more effective pharmacological therapies for schizophrenia, it would be preferable to have reliable preclinical criteria to screen for drugs with the advantageous properties of clozapine.

Results of this investigation suggest that assessment of antipsychotic drug effects on ketamine-induced brain metabolic activation could be a useful preclinical model to assess clozapine-like effects of putative atypical antipsychotics. Both clozapine and olanzapine were effective in blocking ketamine-induced alterations in 2-DG uptake. In contrast, a dose of risperidone, demonstrated to effectively block D$_2$ and 5HT$_2A$ receptors (Janssen et al., 1988; Megens et al., 1994; Arnt, 1995; Zhang and Bymaster, 1999), had no effect on the...
brain metabolic response to ketamine. These data suggest that the observed robust effects of clozapine and olanzapine may not be entirely due to combined D₂/5HT₂A receptor blockade. Although it is likely that D₂ and 5HT₂A receptor antagonism is involved in the effects of clozapine and olanzapine, there may be additional pharmacological actions of the drugs that contribute to their therapeutic properties and activity in experimental models of NMDA receptor hypofunction. It is conceivable that clozapine could have modulatory actions at NMDA receptors, given the proconvulsant proper-

Fig. 2. Effects of olanzapine (5 mg/kg) on ketamine-induced 2-DG uptake. Data are means ± S.E. with four to six rats per group. Rats were injected with olanzapine 30 min before injection of ketamine (25 mg/kg). Saline-saline; saline-ketamine; olanzapine-saline; olanzapine-ketamine. *P < .05 compared with saline-ketamine.

Fig. 3. Autoradiograms of 2-DG uptake at the level of the medial prefrontal cortex showing effects of ketamine (25 mg/kg), olanzapine (10 mg/kg), and clozapine (5 mg/kg). Rats were injected with saline, olanzapine, or clozapine, and 30 min later were treated with saline or ketamine as indicated. MFC, medial prefrontal cortex; ACB, nucleus accumbens. Note the marked ketamine-induced increase in 2-DG uptake in the MFC and ACB and the blockade of this response by olanzapine and clozapine.

Fig. 4. Autoradiograms of 2-DG uptake of the hippocampal formation showing effects of ketamine (25 mg/kg), olanzapine (10 mg/kg), and clozapine (5 mg/kg). Rats were treated as described in Fig. 3. SLM, stratum lacunosum-moleculare; LHB, lateral habenula.
ties of the drug. Although clearly a speculative proposition, an agonistic action of clozapine (and the structurally related drug olanzapine) at NMDA receptors would be a potential mechanism for the blockade of brain metabolic effects induced by ketamine.

Although olanzapine, like risperidone, is a potent D2 and 5HT2A antagonist, the dose of olanzapine required to block effectively ketamine-induced alterations in 2-DG uptake is greater than would be expected if combined 5HT2A/D2 receptor antagonism were solely responsible for actions of the drug in this model. The ED50 values for in vivo receptor occupancy of D2 and 5HT2 receptors by olanzapine are 0.6 mg/kg and 0.15 mg/kg, respectively, although the maximal D2 occupancy was only 70% (Zhang and Bymaster, 1999). In addition, administration of olanzapine i.v. in doses of 1 mg/kg or less completely blocked the effects of amphetamine on midbrain dopamine neuronal firing (a D2-mediated response) (Stockton and Rasmussen, 1996). Regarding functional antagonism of 5HT2 receptors in vivo, the ED50 of olanzapine for blocking 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI)-induced increase in phosphoinositide hydrolysis was 0.1 mg/kg (Zhang and Bymaster, 1999). Therefore, a high degree of both D2 and 5HT2A receptor blockade would be expected at 5 mg/kg, but this dose of olanzapine only partially blocked the effects of ketamine on 2-DG uptake. However, at a dose of 10 mg/kg, olanzapine completely blocked effects of ketamine on 2-DG uptake, suggesting that a lower potency property of the drug may contribute to the observed effects.

Clinical studies of D2 receptor occupancy in relation to therapeutic effects of typical neuroleptics suggest that a threshold of 65 to 70% occupancy must be reached for a satisfactory antipsychotic response (Farde et al., 1992). At the recommended and generally administered maximal doses, 20 mg/day of olanzapine and 6 mg/day of risperidone, D2 occupancy greater than 70% is found (Kapur et al., 1998, 1999; Tauscher et al., 1999). By contrast, effective antipsychotic responses to clozapine are observed at relatively low D2 occupancy (usually 30–60%), which is well below the postulated therapeutic threshold for typical antipsychotics (Nordstrom et al., 1995; Kapur et al., 1999). The relatively low D2 occupancy produced by clozapine probably explains the virtual absence of EPS induced by the drug, because EPS is usually associated with D2 occupancies of 80% and greater (Farde et al., 1992). Therapeutic doses of all three antipsychotics induce a high degree of 5HT2 receptor occupancy that is usually greater than 90% (Farde et al., 1995; Nordstrom et al., 1995; Kapur et al., 1998, 1999). However, the relationship between 5HT2 receptor blockade and therapeutic response is uncertain (Kapur et al., 1999).

The requirement for a relatively high dose of olanzapine to block ketamine-induced brain metabolic activation is interesting in light of recent clinical data suggesting that doses of olanzapine greater than those required to produce high levels of D2 and 5HT2 receptor occupancy (greater than 75 and 90%, respectively) may be more effective in treating schizophrenic symptoms (J. Volavka, J.A.L., and J. McEvoy, unpublished data). For example, effective antipsychotic responses to olanzapine in doses of 30 to 80 mg/day have been observed in patients who failed to respond to the recommended maximal dose of 20 mg of olanzapine (Sheitman et al., 1997; Fanous and Lindenmayer, 1999; Heimann, 1999; Mountjoy et al., 1999; Reich, 1999). The requirement for these higher doses of olanzapine to achieve an antipsychotic action suggests that pharmacological properties (of lower potency), in addition to D2 and 5HT2 receptor blockade, could play a role in the therapeutic effects of higher doses of the drug.

The effects of the antipsychotic drugs in the ketamine challenge 2-DG model are consistent with behavioral models involving NMDA antagonists. In monkeys, clozapine reduced performance deficits, which were induced by chronic PCP treatment, in a cognitive task sensitive to prefrontal cortex function (Jentsch et al., 1997). Also, clozapine and olanzapine blocked PCP-induced deficits in social interactions, whereas haloperidol and risperidone were ineffective (Corbett et al., 1995). In the prepulse inhibition (PPI) paradigm, clozapine and olanzapine blocked NMDA antagonists-induced deficits in PPI (Bakshi et al., 1994; Bakshi and Geyer, 1995; Swerdlov et al., 1996). However, in accord with our present and previous findings (Duncan et al., 1998b), neither risperidone nor haloperidol blocked the disruption of PPI by PCP or MK-801 in Sprague-Dawley rats (Swerdlow et al., 1996;

**Fig. 5.** Effects of olanzapine (10 mg/kg) and clozapine (5 mg/kg) on ketamine-induced 2-DG uptake. Data are means ± S.E. with eight to ten rats per group. ■, saline-saline; □, saline-ketamine; ▪, olanzapine-saline; ○, olanzapine-ketamine; □, clozapine-saline; ▪, clozapine-ketamine. *P < .05 compared with saline-ketamine.
Varty et al., 1999). Interestingly, the selective 5HT2A receptor antagonist, M100907, was effective in blocking MK-801-induced PPI deficits (Varty et al., 1999), and it will be of interest to examine this drug in the ketamine challenge 2-DG paradigm.

Differential effects of typical and atypical antipsychotics have also been demonstrated on electrophysiological responses to NMDA and NMDA antagonists. Clozapine potentiated electrophysiological activation of neurons in the medial prefrontal cortex induced by stimulation of the corpus callosum (Arvanov et al., 1997). By contrast, haloperidol inhibited responses in the same experimental paradigm. These data are consistent with the opposite effects of clozapine and haloperidol on ketamine-induced 2-DG uptake (Duncan et al., 1998b). However, when effects of haloperidol and clozapine were examined on responses induced by direct application of NMDA, both haloperidol and clozapine potentiated NMDA-evoked responses, although clozapine was more potent in this action (Arvanov et al., 1997). The differential effects observed in the NMDA-evoked responses, in comparison with excitation induced by stimulation of the corpus callosum, were explained by the observation that haloperidol, but not clozapine, inhibited α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-activated responses.

In accord with the action of clozapine to potentiate NMDA-evoked electrophysiological responses, this atypical antipsychotic was able to reverse the inhibitory effect of PCP in the prefrontal cortex (Wang and Liang, 1998). However, haloperidol and raclopride (a potent D2 antagonist) did not prevent the PCP-induced inhibition of NMDA-mediated electrophysiological activation (Wang and Liang, 1998). Also, clozapine, but not haloperidol, was able to prevent the functional hyperactivity induced by subchronic administration of PCP in rats (Arvanov and Wang, 1999). These electrophysiological findings are consistent with the ability of clozapine to block ketamine-induced increases in 2-DG uptake.

Limited clinical information is available regarding the effects of antipsychotic drugs on responses to ketamine in schizophrenic patients, but existing data are consistent with results from experimental animals. Patients on haloperidol exhibited greater increases in ketamine-induced psychosis ratings relative to baseline, compared with a haloperidol-free condition (Lahti et al., 1995). In contrast, clozapine treatment blunted ketamine-induced increases in thought disturbance in schizophrenic patients (Malhotra et al., 1997). These findings in humans parallel the observed effects of haloperidol and clozapine on responses to NMDA antagonists in select preclinical models and suggest that such preclinical paradigms could be useful for exploring the neurobiological basis of atypical antipsychotic drug action. Furthermore, the analogous nature of the autoradiographic assessment of 2-DG uptake and imaging brain activity by functional magnetic resonance imaging and positron emission tomography offer a unique opportunity for translational studies to explore effects of antipsychotic drugs on brain metabolic responses to ketamine in humans.

References

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