Probing GABA Receptor Function in Schizophrenia with Iomazenil

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Several lines of evidence from post-mortem, brain imaging, and genetic studies in schizophrenia patients suggest that Gamma-amino butyric acid (GABA) deficits may contribute to the pathophysiology of schizophrenia. Pharmacological induction of a transient GABA-deficit state has been shown to enhance vulnerability of healthy subjects to the psychotomimetic effects of various drugs. Exacerbating or creating a GABA deficit was hypothesized to induce or unmask psychosis in schizophrenia patients, but not in healthy controls. To test this hypothesis, a transient GABA deficit was pharmacologically induced in schizophrenia patients and healthy controls using iomazenil, an antagonist and partial inverse agonist of the benzodiazepine receptor. In a double-blind, randomized, placebo-controlled study, clinically stable chronic schizophrenia patients ($n = 13$) received iomazenil ($3.7 \mu\text{g}$ administered intravenously over 10 min). Psychosis was measured using the Brief Psychiatric Rating Scale and perceptual alterations were measured using the Clinician Administered Dissociative Symptoms Scale before and after iomazenil administration. These data were compared with the effects of iomazenil in healthy subjects ($n = 20$). Iomazenil produced increases in psychotic symptoms and perceptual alterations in schizophrenia patients, but not in healthy controls. The greater vulnerability of schizophrenia patients to the effects of iomazenil relative to controls provides further support for the GABA-deficit hypothesis of schizophrenia.

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INTRODUCTION

Converging lines of evidence, including postmortem (Benes, 2000; Benes and Berretta, 2001; Benes *et al*, 1996; Hashimoto *et al*, 2003; Lewis *et al*, 2005; Ohnuma *et al*, 1999; Volk *et al*, 2000; Volk and Lewis, 2002; Volk *et al*, 2002; Woo *et al*, 1998), genetic (reviewed by Charych *et al* (2009), and brain imaging studies (Ball *et al*, 1998; Busatto *et al*, 1997; Schroder *et al*, 1997; Verhoeff *et al*, 1999; Yoon *et al*, 2010), suggest that dysfunction of the gamma-amino butyric acid (GABA) system contributes to the pathophysiology of schizophrenia. In postmortem studies of schizophrenic patients, alterations in GABAergic transmission have been shown in many ways, including (1) reduced mRNA levels for the GABA-synthesizing enzyme glutamic acid decarboxylase-67 (Impagnatiello *et al*, 1998; Volk *et al*, 2000), (2)

decreased density of axon cartridges of chandelier neurons (Woo *et al*, 1998), (3) decreased gene expression of the GABA membrane transporter-1 (Ohnuma *et al*, 1999; Volk and Lewis, 2002), (4) increased density of GABA-A receptors (Benes *et al*, 1996), (5) elevated density of α_1 - (Impagnatiello *et al*, 1998; Ohnuma *et al*, 1999) and α_2 -subunit-containing GABA-A receptors at pyramidal neuron axon segments (Volk *et al*, 2002), (6) decreased Reelin mRNA, which is preferentially expressed in GABAergic interneurons (Impagnatiello *et al*, 1998), and (7) decreased levels of ankyrin-G, a membrane protein that anchors the GABA receptor complex onto initial axonal segments of pyramidal cells in the area of chandelier cell synapses in superficial cortical area (Cruz *et al*, 2009). Many of these findings appear to be specific to schizophrenia (Volk and Lewis, 2002). Besides post-mortem data, some *in vivo* brain imaging (SPECT) studies suggest reduced benzodiazepine (BZ) receptor binding in schizophrenia (Ball *et al*, 1998; Busatto *et al*, 1997; Schroder *et al*, 1997).

GABAergic deficits described above may contribute to the pathophysiology of psychosis by several mechanisms. While it is out of the scope of this paper to discuss all the possible mechanism, a few putative mechanism are discussed below.

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One mechanism may involve the critical role that GABA interneurons have in synchronizing neural activity and, consequently, in information processing (reviewed in Uhlhaas and Singer, 2010). Sensory perception, emotion, attention, and memory, which are characteristically disturbed in schizophrenia, are based on distributed processes among multiple cortical and subcortical regions. It has been proposed that the neural assemblies representing these processes are functionally 'bound' together by synchronous high-frequency oscillatory activity to create a coherent cortical representation (Engel and Singer, 2001; Singer, 1999; Singer and Gray, 1995; Tallon-Baudry, 2003; Varela, 2001; Varela, 1995). The spike timing of pyramidal cells and the tuning of neuronal rhythms are largely governed by GABAergic interneurons. Loss of the inhibitory influence of GABAergic interneurons from cell loss or reduced function could lead to a loss of synchronization of pyramidal cell activity, resulting in the loss of associative functions, disruption of normal gating mechanisms, and eventually psychotic symptoms. Consistent with this hypothesis, several lines of evidence suggest that dysfunctional synchronized oscillatory neuronal activity may contribute to the pathophysiology of the perceptual and cognitive abnormalities in schizophrenia (Lewis *et al.*, 2005; Uhlhaas and Singer, 2010).

Another potential mechanism by which GABA contribute to the pathophysiology of psychosis may involve the interactions between the GABA and dopamine (DA) systems. Converging lines of evidence suggest that the activity of DA neurons in the VTA is under tonic inhibitory control by GABA-A receptors (Fritschy and Mohler, 1995; Pirker *et al.*, 2000; Waldvogel *et al.*, 2008). Specifically relevant to this study, systemic administration of GABA-A receptor inverse agonist, FG7142 has been shown to activate VTA neurons (Murphy *et al.*, 1996). Interestingly, FG7142-induced VTA activation was reversed by DA receptor antagonists. It should be noted that FG7142 and iomazenil are both inverse agonists. Therefore, a reduction in GABAergic transmission by GABA-A receptors, as would be the case with iomazenil, in the presence of pre-existing dysregulation of DA function, as is the case in schizophrenia, would be expected to further disinhibit DA systems, leading to a worsening of the DA-related symptoms in schizophrenia (Abi-Dargham *et al.*, 1998; Laruelle *et al.*, 1996). We acknowledge that this study does not directly test whether iomazenil increases neural synchrony deficits or DA dysregulation. Rather, the study measures a very distal outcome—psychotic symptoms that could result from an exacerbation of DA dysregulation or altered neural synchrony. The current report describes how pharmacological induction of GABAergic deficits, with iomazenil, increases psychosis.

Pharmacological induction of GABAergic deficits increases vulnerability to psychosis. Iomazenil (Ro 16-0154) is an iodine analog of the BZ receptor competitive antagonist flumazenil. Iomazenil has high affinity and selectivity for BZ receptors ($K_d = 0.5$ nM) (Johnson *et al.*, 1990). Some of its pharmacological properties are comparable with those of flumazenil (Beer *et al.*, 1990). However, unlike the competitive antagonist flumazenil, which blocks the effects of BZ agonists but lacks intrinsic pharmacological effects (Hunkeler *et al.*, 1981), inverse agonists have intrinsic pharmacological effects opposite to those of BZs

(Tallman and Gallager, 1985). In preclinical studies, iomazenil has been shown to behave as a BZ receptor competitive antagonist with inverse agonist effects (Beer *et al.*, 1990; Roche; Schubiger and Hasler, 1989). Similarly, clinical studies demonstrate that iomazenil has anxiogenic effects and at higher doses has proconvulsant effects (Randall, personal communication) that are consistent with inverse agonist activity at BZ receptors. Iomazenil produces a net deficit in GABA function.

Iomazenil has been shown to increase the psychotomimetic effects of the 5-HT₂ partial agonist 1-(m-chlorophenyl)piperazine (m-CPP) in healthy subjects (D'Souza *et al.*, 2006). Thus, although neither iomazenil nor m-CPP alone induces psychosis, the combination of iomazenil followed by m-CPP causes measurable psychotic symptoms in healthy subjects. Similarly, unpublished preliminary data from our laboratory suggest that GABA deficits induced by iomazenil pretreatment may also increase the psychotomimetic effects of low-dose amphetamine (0.1 mg/kg, intravenous (IV) infusion over 1 min), which by itself does not induce psychotic symptoms, and delta-9-tetrahydrocannabinol (Δ^9 -THC) in healthy subjects. Collectively, these studies suggest that the known vulnerability of schizophrenia patients to the psychotomimetic effects of amphetamine (Laruelle *et al.*, 1999; Laruelle *et al.*, 1996) and Δ^9 -THC (D'Souza *et al.*, 2005) might result from pre-existing GABA deficits.

Although there is strong support for the existence of a GABA deficit in schizophrenia, the proportion of schizophrenia patients with this deficit is not known. The limited data available suggest that only 50% of schizophrenia patients have lower GABA levels than the lowest level found in healthy normal controls (Yoon *et al.*, 2010). Furthermore, BZ augmentation reduces psychosis in only 30–50% of schizophrenia patients (Wolkowitz and Pickar, 1991).

We hypothesized that if GABA deficits contribute to an increased propensity toward psychosis in schizophrenia, then enhancement of these deficits should exacerbate psychotic symptoms in some schizophrenia patients, but not in healthy normal controls.

MATERIALS AND METHODS

Participants

Thirteen chronic, stable schizophrenia patients were recruited and compared with data from 20 healthy normal controls from a previous study (D'Souza *et al.*, 2006). Diagnosis was confirmed by SCID-III-R or SCID-IV. Inclusion and exclusion criteria for both studies were identical other than diagnosis. Included were men, 18–70 years old, who were able to provide informed consent; excluded were those with other Axis-I disorders; substance abuse (by history or urine toxicology); treatment with BZs in the previous week, clozapine, or low-potency anti-psychotics (thorazine, thioridazine, mesoridazine); unstable medical conditions; active neurological illness requiring treatment; seizure history; abnormal baseline EKG; suboptimally controlled psychosis (defined as >16 on the four-key positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS)); high risk for violence or suicide; and women, as the teratogenic potential of iomazenil is

unknown. Potential subjects underwent a thorough medical and psychiatric history, complete physical examination, and a battery of laboratory tests including EEG, EKG, blood chemistry (CBC, BUN, creatinine, fasting blood glucose, electrolytes, liver and thyroid function tests), and urinalysis.

The study was conducted at the Neurobiological Studies Unit (VA Connecticut Healthcare System, West Haven, CT) with the approval of the Institutional Review Boards of VA Connecticut Healthcare System and Yale University School of Medicine. Subjects were recruited by word of mouth, clinician referral, and public advertisement. Subjects were compensated \$100 per test day for participating. Confidentiality of study data was assured. Data on the effects of iomazenil in healthy subjects were taken from the iomazenil-only and placebo-only test days of a published study of the interactions of iomazenil and m-CPP (D'Souza *et al*, 2006). These studies were carried out in the same setting, by the same investigators and raters, during the same time period, using almost identical protocols.

Experimental Design

Subjects completed two test days, during which they received placebo or active (3.7 µg/kg) iomazenil over 10 min in random, counterbalanced order under double-blind conditions. Test days were separated by at least 72 h in order to minimize any carryover effects.

Schedule of testing

The detailed schedule of test procedures is described elsewhere (D'Souza *et al*, 2006). Subjects were required to refrain from using alcohol, street drugs, psychotropic medications, or caffeinated beverages for 2 weeks before testing and throughout the entire study. Urine toxicology was conducted on each test day to rule out recent drug use; a positive screen resulted in exclusion from the study.

After obtaining IV access and two sets of baseline assessments, subjects were administered active IV iomazenil or placebo (saline over a 10-min period). Behavioral ratings were conducted before (−55 to −30 min) and after (+10 to +30 min) the administration of iomazenil.

Measures

Psychotic symptoms were measured using the four-key positive symptom subscale of the BPRS, which has items for hallucinatory behavior, conceptual disorganization, unusual thought content, and suspiciousness (Overall and Gorham, 1962; Woerner *et al*, 1988). Perceptual alterations were measured using the Clinician Administered Dissociative Symptoms Scale (CADSS) (Bremner *et al*, 1998), a scale consisting of 19 self-report items and 8 clinician-rated items (0, not at all; 4, extremely), that evaluates aspects of altered environmental perception, time perception, body perception, feelings of unreality, and memory impairment. The scale has been shown to be sensitive to the effects of other psychoactive drugs, including ketamine and THC (D'Souza *et al*, 2004; Krystal *et al*, 1994). Anxiety was measured using the clinician-rated anxiety item of the BPRS, which is sensitive to iomazenil effects (D'Souza *et al*, 2006). The same research assistant rated both days of a subject and

the same group of staff rated both schizophrenia patients and healthy controls. Interrater reliability was assessed every 1–2 months, and intraclass coefficients for the BPRS and CADSS were consistently >0.85.

Statistical Analysis

All statistical analyses were performed using SPSS Version 17. Demographic data were compared using independent *t*-tests. As the BPRS and CADSS data were not normally distributed in controls, and as there were obvious baseline differences between the two groups, peak change from baseline was used in the analysis of these behavioral outcome variables. These variables were analyzed using repeated analysis of variance (ANOVA) with iomazenil (active *vs* placebo) as within-subject factor and group (schizophrenia *vs* control) as between-subject factors.

RESULTS

Schizophrenia patients were significantly older, less educated, and less employed than control subjects (Table 1).

Positive Symptoms

There was a significant main effect of drug (iomazenil *vs* placebo, $F(1,31) = 7.26$, $p = 0.011$) and drug-by-group interaction ($F(1,31) = 5.84$, $p = 0.022$), but no main effect of group (schizophrenia *vs* control, $F(1,31) = 0.20$, $p = 0.66$) on peak change in four-key BPRS scores. Although iomazenil did not have any significant effect on four-key BPRS scores in controls (0.1 ± 0.31 for placebo and 0.15 ± 0.67 for iomazenil, $F(1,12) = 0.09$, $p = 0.77$), it produced significant increases in schizophrenia subjects (-0.46 ± 0.97 for placebo and 0.46 ± 1.66 for iomazenil, $F(1,12) = 6.35$, $p = 0.027$, $P2 = 0.35$; Figure 1).

Overall Symptoms

There were no significant effects of group ($F(1,31) = 3.35$, $p = 0.08$), drug ($F(1,31) = 0.87$, $p = 0.36$), or drug $\times$ group interaction ($F(1,31) = 0.29$, $p = 0.60$) in total BPRS score peak change.

Perceptual Alterations

There was a significant main effect of drug (iomazenil *vs* placebo, $F(1,31) = 10.08$, $p = 0.003$) and a drug-by-group interaction ($F(1,31) = 5.05$, $p = 0.032$) but no main effect of group (schizophrenia *vs* control, $F(1,31) = 0.004$, $p = 0.95$) on peak change in CADSS total scores. Although iomazenil did not have any significant effect on peak change in CADSS total scores in controls (0.35 ± 1.04 for placebo and 0.60 ± 1.76 for iomazenil, $F(1,12) = 0.80$, $p = 0.38$), it produced significant increases in schizophrenia subjects (-0.23 ± 1.17 for placebo and 1.23 ± 1.42 for iomazenil, $F(1,12) = 8.08$, $p = 0.015$, $\eta_p^2 = 0.40$; Figure 2). There were no significant correlations between the peak change in CADSS and BPRS four-key positive symptom scores for each drug condition.

Table 1 Demographic Characteristics

	Schizophrenia (n = 13)	Controls (n = 20)	Comparison
Age (years)*	45.7 ± 10.6	37.9 ± 9.9	$t = 2.157$, $df = 31$, $p = 0.039$
M/F	13/0	20/0	NS
Ethnicity (Caucasian/African American/other)	6 Caucasian, 6 African American, 1 Hispanic	13 Caucasian, 5 African American, 2 Hispanic	$\Phi = 0.219$, $p = 0.452$
Employment status**	2 of 13 employed	All employed	$\Phi = .877$, $p < 0.001$
Education (years)**	12.4 ± 1.99	15.9 ± 1.86	$t = -4.439$, $df = 26$, $p < 0.001$
<i>BPRS baseline scores</i>			
Total**	30.69 ± 6.36	19.05 ± 1.19	$t = 8.043$, $df = 31$, $p < 0.001$
Positive symptoms**	8.38 ± 4.11	4.05 ± .22	$t = 4.743$, $df = 31$, $p < 0.001$
Anxiety baseline*	1.69 ± 0.79	1.28 ± .60	$t = 2.133$, $df = 31$, $p = 0.041$
CADSS baseline score*	1.54 ± 2.70	0.10 ± .31	$t = 2.383$, $df = 31$, $p = 0.024$
Schizophrenia subtype (DSM-III-R)	Chronic paranoid—11 Chronic undifferentiated—1 Chronic disorganized—1		
Age of onset (years)	28.75 ± 10.33		
Antipsychotic medication	Fluphenazine—2 Fluphenazine decanoate—2 Haloperidol—1 Perphenazine—1 Risperidone—1 Olanzapine—1 Unmedicated—3		
Antipsychotic dose (mg) in chlorpromazine equivalents	668 ± 686 mg		

* $p < 0.05$, ** $p < 0.001$.

Data presented as means ± SD.

Anxiety

Baseline BPRS anxiety scores were comparable between placebo day and iomazenil day in both schizophrenia (Table 1). There were no significant effects of group ($F(1,31) = 0.03$, $p = 0.87$), drug ($F(1,31) = 0.73$, $p = 0.40$), or drug $\times$ group interaction ($F(1,31) = 0.73$, $p = 0.40$) on the peak change of BPRS anxiety subscale.

DISCUSSION

Consistent with the GABA-deficit hypothesis of schizophrenia, iomazenil increased psychotic symptoms and perceptual alterations in schizophrenia patients, but not in controls. The effects of iomazenil were modest; effect size was small ($\eta_p^2 = 0.35$). It should be noted that the schizophrenia patients were symptomatically stable and taking D_2 -receptor antagonists, which could have blunted their response to iomazenil. Furthermore, as GABA deficits likely contribute to a vulnerability to psychosis rather than being intrinsically pro-psychotic, the small effect of iomazenil was not unexpected, and is noteworthy especially as iomazenil did not have any effects in healthy normal subjects. The notion that GABA deficits increase the vulnerability to psychosis is illustrated by the observation that although m-CPP, a partial serotonin $2C$, $1A$, $1B$, and $1D$ receptor

agonist, did not produce psychosis in healthy subjects when administered alone, it did so when administered after iomazenil (D'Souza *et al*, 2006).

Iomazenil increased psychosis and perceptual alterations in about 50% of schizophrenia patients (Figures 1 and 2), supporting the hypothesis that GABA deficits may be present only in a subgroup. As discussed elsewhere, GABA deficits may increase vulnerability to pro-psychotic drugs. Thus, the hypothesis that only a subgroup of schizophrenia patients have GABA deficits might explain why only a subgroup of schizophrenia patients experience worsened psychosis in response to m-CPP (Iqbal *et al*, 1991; Krystal *et al*, 1993), amphetamine (Lieberman *et al*, 1987), ketamine (Lahti *et al*, 1995; Malhotra *et al*, 1997), or Δ^9 -THC (D'Souza *et al*, 2005).

The use of iomazenil to interrogate GABA function in schizophrenia is novel. This study has a number of strengths, including a double-blind, placebo-controlled design, and use of well-validated measures. It also has some limitations. First, the sample size was relatively small, thus confirmatory study with a larger sample size may be necessary. The groups were not matched for treatment with antipsychotic drugs. However, treatment with antipsychotic medications (DA D_2 receptor antagonists) would be expected to blunt the response of schizophrenia patients to iomazenil, obscuring group differences rather than

Figure 1 Peak change in 4-key BPRS.

enhancing them. Further studies comparing schizophrenia patients on and off antipsychotic medications will need to be conducted. The groups were also not matched by age. However, there is no reason to presume that older subjects show increased response to iomazenil, and a significant response to iomazenil persisted within the schizophrenic group even when age was used as a covariate in the analysis. As only men were studied, because the teratogenic potential of iomazenil is unknown, the results may not generalize to women. Finally, on the basis of other evidence suggesting GABA deficits in schizophrenia (Lewis and Hashimoto, 2007), the study presumes that any differential responses to iomazenil reflect a trait rather than a state. However, this will need to be confirmed by studying the effects of iomazenil in different stages of schizophrenia.

In conclusion, iomazenil exacerbated psychosis in some schizophrenia patients. Identifying patients with GABA deficits is of therapeutic relevance, as a number of drugs can be used to enhance GABA function, such as MK-077, BZs, tiagabine, and vigabatrin. The findings of this small study justify future studies with iomazenil in a larger sample with more proximal measures of GABA function (such as electrophysiological indices of neural synchrony) that might be more sensitive in assessing GABA deficits in schizophrenia. Further studies should also compare schizophrenia patients on and off antipsychotic medications, and compare different stages of schizophrenia to verify that any observed GABA deficits are stable over time.

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Figure 2 Peak change in CADSS total score.

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