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Decreased density of serotonin 2A receptors in the superior temporal gyrus in schizophrenia - a postmortem study

Abstract

The superior temporal gyrus (STG) is strongly implicated in the pathophysiology of schizophrenia, particularly with regards to auditory hallucinations. In this study, using in situ quantitative autoradiography in postmortem tissue, we investigated the binding of the [3H]ketanserin to 5-HT_{2A} receptors and [3H] mesulergine to 5-HT_{2C} receptors in the left STG of 8 male schizophrenic patients compared to 8 control subjects. A strong [3H]ketanserin binding was observed in the STG, however there was a very weak [3H] mesulergine binding in the STG. A significant decrease in binding of [3H]ketanserin was clearly observed in schizophrenia patients in comparison with control subjects. There were no significant correlations between 5-HT_{2A} binding density and age, postmortem intervals, or brain pH. These results suggest that the alterations of the 5-HT_{2A} receptors contribute to the pathophysiology of the STG in schizophrenia. Furthermore, there is a clear tendency for a positive correlation between 5-HT_{2A} and muscarinic M1 receptor bindings, and for negative correlations between 5-HT_{2A} and GABA_A receptor bindings and between muscarinic M1 and GABA_A receptor bindings. This provides a possible mechanism of auditory hallucinations through interactions between 5-HT_{2A}, acetylcholine muscarinic and GABA transmissions in the STG in schizophrenia.

Keywords

Decreased, density, serotonin, receptors, superior, temporal, gyrus, schizophrenia, postmortem, study

Disciplines

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Title:

DECREASED DENSITY OF SEROTONIN 2A RECEPTORS IN THE SUPERIOR TEMPORAL GYRUS IN SCHIZOPHRENIA-A POSTMORTEM STUDY

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Abstract:

The superior temporal gyrus (STG) is strongly implicated in the pathophysiology of schizophrenia, particularly with regards to auditory hallucinations. In this study, using *in situ* quantitative autoradiography in postmortem tissue, we investigated the binding of the [³H]ketanserin to 5-HT_{2A} receptors and [³H]mesulergine to 5-HT_{2C} receptors in the left STG of 8 male schizophrenic patients compared to 8 control subjects. A strong [³H]ketanserin binding was observed in the STG, however there was a very weak [³H]mesulergine binding in the STG. A significant decrease in binding of [³H]ketanserin was clearly observed in schizophrenia patients in comparison with control subjects. There were no significant correlations between 5-HT_{2A} binding density and age, postmortem intervals, or brain pH. These results suggest that the alterations of the 5-HT_{2A} receptors contribute to the pathophysiology of the STG in schizophrenia. Furthermore, there is a clear tendency for a positive correlation between 5-HT_{2A} and muscarinic M1 receptor bindings, and for negative correlations between 5-HT_{2A} and GABA_A receptor bindings and between muscarinic M1 and GABA_A receptor bindings. This provides a possible mechanism of auditory hallucinations through interactions between 5-HT_{2A}, acetylcholine muscarinic and GABA transmissions in the STG in schizophrenia.

Key words: Schizophrenia; 5-HT_{2A} receptor; GABA receptor; Muscarinic receptor;
Superior temporal gyrus

Abbreviations: PMI, postmortem intervals; STG, superior temporal gyrus; 5-HT, serotonin 2; cc, corpus callosum; IG, insular gyrus; lf, lateral fissure; MTG, medial temporal gyrus; sts, superior temporal sulcus; Th, thalamus.

1. Introduction

There is strong evidence that serotonin 2 (5-HT₂) receptors are involved in the neuropathology and treatment of schizophrenia. There is a clear association between polymorphism of the 5-HT_{2A} receptor gene and schizophrenia (Abdolmaleky et al., 2004; Ott et al., 2005; Saiz et al., 2007). Postmortem studies have also shown that 5-HT_{2A} receptor mRNA is reduced in the dorsolateral prefrontal and anterior cingulate cortices, hippocampus, and striatum in schizophrenia (Burnet et al., 1996; Lopez-Figueroa et al., 2004). Recently Hurlemann and colleagues revealed that schizophrenia subjects at prodromal or at-risk mental states have decreased 5HT_{2A} receptor densities in the dorsolateral prefrontal and posterior insular cortices, amygdalae, hippocampus and striatum (Hurlemann et al., 2005; Hurlemann et al., 2008). Autoradiographic binding studies in postmortem tissue have also found a significant decrease in the density of [³H]ketanserin binding to the 5-HT_{2A} receptor in the prefrontal and planum temporal cortices, as well as the hippocampus (Burnet et al., 1996; Dean and Hayes, 1996; Pralong et al., 2000; Scarr et al., 2004; Matsumoto et al., 2005). However, some controversial findings have also been reported. For example, a number of studies did not reveal the association between polymorphism of the 5-HT_{2A} receptor gene and schizophrenia (Verga et al., 1997; Li et al., 2006). Some earlier PET scan studies did not find any abnormality of 5-HT_{2A} receptor density in schizophrenia (Trichard et al., 1998; Verhoeff et al., 2000). A recent PET study in neuroleptic-naïve first episode schizophrenia has found there was no changes in 5-HT_{2A} receptor binding in the cortical regions, although an increase in the caudate nucleus was detected (Erritzoe et al., 2008). On the other hand, a postmortem study did not show any changes of [³H]ketanserin binding density in the

hippocampus, although it observed a binding decrease in the prefrontal cortex (Matsumoto et al., 2005).

There is much less information available on the possible pathological roles of 5-HT_{2C} in schizophrenia. Editing of 5-HT_{2C} receptor RNA has been reported to be reduced in the frontal cortex (left Brodmann's area 46) in schizophrenia, which indicates a potential alteration of this receptor (Sodhi et al., 2001). To date, no 5-HT_{2C} receptor binding study has been performed on postmortem tissue. Therefore, further study is necessary to verify the pathological mechanisms of 5-HT_{2A} and 5-HT_{2C} receptors in schizophrenia, particularly to investigate whether alteration of 5-HT_{2A} receptors occurs in other brain regions involved in the pathology of schizophrenia.

The superior temporal gyrus (STG) is strongly implicated in the pathophysiology of schizophrenia, particularly with regards to auditory hallucinations (Silbersweig et al., 1995; Kim et al., 2003; Gaser et al., 2004). However, there are only a few studies on 5-HT₂ receptors in the STG in schizophrenia. By assessing the loudness dependence of auditory evoked potentials, it has been shown that dysfunction of 5-HT₂ receptors may cause deficits of auditory processing in schizophrenia (Juckel et al., 2003). A significant decrease in 5-HT_{2A} receptor mRNA expression has been found in the STG in schizophrenia (Burnet et al., 1996). It is also interesting that 5-HT_{2A} and 5-HT_{2C} receptors are known to be important target sites of hallucinogens like lysergic acid (LSD) (Nichols, 2004). Furthermore, 5-HT_{2A} is the target of several atypical antipsychotics (such as clozapine and olanzapine) that have been proven to be effective in the treatment

of schizophrenia (Schmidt et al., 1995; Tyson et al., 2004). In this study, we have examined 5-HT_{2A} (using [³H]ketanserin) and 5-HT_{2C} receptor (using [³H]mesulergine) bindings in the STG of schizophrenic patients and control subjects using quantitative autoradiography. Combined with data from previous studies (Deng and Huang, 2005, 2006), the relationships between 5-HT_{2A}, muscarinic and GABA_A receptors were also examined.

2. Methods and Materials

2.1 Subjects and preparation of postmortem brain tissue

Postmortem brain tissue was obtained from the NSW Tissue Resource Centre (TRC), including 8 schizophrenic patients and 8 controls matched by age, gender (all males), race (all Caucasian Australian) and postmortem intervals (PMI). The diagnosis of schizophrenia was established after review of all available medical records by using the Diagnostic Instrument for Brain Studies (Keks et al., 1999). The diagnosis of schizophrenia was confirmed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (Sheedy et al., 2008). All schizophrenic subjects had a positive rating in auditory hallucinations, in which a positive rating was defined as experiencing auditory hallucinations twice per month. For control cases, medical records were reviewed to exclude any history of major psychiatric disorders and, if necessary, to exclude possible psychopathology. Cases which had a significant history of neurological disorder, head injury, or with PMI over 48 hours were excluded. The details of demographic and clinical data of all subjects are presented in Table 1 (Deng and Huang, 2005). This study was approved by the Human Research Ethics Committee, University of

Wollongong, Australia, and complied with the NHMRC National Statement on Ethical Conduct in Research Involving Humans 1999.

In all cases, the tissue was taken from the left-brain hemisphere of the superior temporal gyrus (Brodmann's area 22). The right-brain hemispheres were fixed with formalin and therefore were not available for this study. Once brain tissue was collected, it was immediately dissected into small blocks (10 mm thick) and stored in a -80°C freezer until sectioning. The brain tissue was cut into $14\ \mu\text{m}$ sections using a cryostat at -17°C and the sections were mounted on polysine-coated slides. All sections were stored at -20°C until they were thawed at room temperature prior to incubation. For each case, four sections were processed for total binding and two sections for non-specific binding for each radioligand. All sections from both schizophrenia and control cases were processed simultaneously to minimize experimental variance. All of the following procedures for autoradiography and quantitative analysis were performed while blind of diagnosis.

2.2 Binding to 5-HT_{2A} receptors

Binding of [³H]ketanserin (88 Ci/mmol; PerkinElmerTM Life Sciences, Boston) to 5-HT_{2A} receptors was performed as previously described from our group (du Bois et al., 2006). In brief, sections were pre-incubated in 170mM Tris-HCl buffer (pH 7.4) for 15 mins at room temperature (RT). Sections were then incubated for 120 mins at RT in the same buffer containing 4nM [³H]ketanserin in the presence (non-specific binding) or absence (total binding) of 2 μM spiperone. After incubation, the sections were washed in ice-cold buffer (2x10 mins), dipped in distilled water and air dried.

2.3 Binding to 5-HT_{2C} receptors

Binding of [³H]mesulergine (84 Ci/mmol; Amersham Biosciences, Buckinghamshire) to 5-HT_{2C} receptors was performed as previously described from our group (du Bois et al., 2006). In brief, sections were pre-incubated in 170mM Tris-HCl buffer (pH 7.4) for 15 mins at RT. Sections were then incubated for 120 mins at RT in the same buffer containing 5nM [³H]mesulergine. Non-specific binding was determined with the addition of 100 nM spiperone and 1 μM mianserin. After incubation, the sections were washed in ice-cold buffer (2x10 mins), dipped in distilled water and air dried.

2.4 Quantification and Statistical analysis

Autoradiographic images were taken using a Beta Imager (BioSpace, Paris) as previously described (Deng and Huang, 2005). In this procedure, sections on slides were placed directly into a beta-imager for scanning for 3.5 h at a high-resolution setting. The levels of bound radioactivity in the brain sections were directly determined by counting the number of β-particles emerging from the tissue sections. Quantitative analysis of these images was performed using β-Image Plus (version 4; BioSpace, Paris). The radioligand binding signal was expressed in counts per minute per square millimetre (cpm/mm²) and was then converted to nCi/mg tissue equivalents (nCi/mg TE) with the use of standards. The specific binding was calculated by total binding minus non-specific binding.

The data were analyzed statistically using the SPSS 15.0 program (Chicago, IL). Comparisons between the two groups (schizophrenia and control) on radioligand binding, age, PMI, and brain pH were made using Student *t*-test. Analysis of covariance (ANCOVA) was performed for controlling age, PMI and brain pH in each radioligand binding. Pearson correlation was used to assess the relationship between binding density and age, brain pH, PMI, and final recorded antipsychotic drug use (FRD). To test whether a drug history affected the binding density, binding data between substance and non-substance users were analysed using Mann-Whitney U test. *P* values less than 0.05 (2-tailed) were considered significant.

3. Results

3.1 [³H]ketanserin and [³H]mesulergine bindings

There were no significant differences in age, PMI, and brain pH between the schizophrenia and control groups (all $p > 0.05$; Table 1). A high density of [³H]ketanserin binding was observed in the middle layers of the STG corresponding to layers III-V (Fig. 1) in both schizophrenic and non-schizophrenic subjects. In contrast, there was a very low level of specific binding of [³H]mesulergine in the STG, which therefore limited further analysis of [³H]mesulergine binding in the STG.

Compared to the control group, the schizophrenia group had a significant 37% decrease in [³H]ketanserin binding density (Mean±SEM, schizophrenia 14.77±2.76 fmole/mg TE vs control 23.58±2.678 fmole/mg TE; $F_{1,12}=5.25$, $p=0.04$). As shown in Table 1, half of the schizophrenia patients had a drug abuse history with polydrug use. The [³H]ketanserin binding densities in the tissues from these substance users (15.26±5.51

fmole/mg TE) were not significantly different from the non-substance users (14.27 ± 2.30 fmole/mg TE, $p > 0.05$). There were no significant effects of age ($F_{1,12} = 0.51$, $p = 0.49$), PMI ($F_{1,12} = 0.15$, $p = 0.71$) and brain pH ($F_{1,9} = 1.06$, $p = 0.33$). Furthermore, in the schizophrenic cases, there were no significant correlations between [^3H]ketanserin binding density and FRD ($r = -0.13$, $p = 0.76$).

3.2 Correlations among 5-HT_{2A}, muscarinic M1 and GABA_A receptor bindings

Using the same cohort of subjects, we had previously found decreased densities of muscarinic M1 ([^3H]pirenzepine binding) and M2/M4 ([^3H]AF-DX384 binding) receptors and increased GABA_A receptor ([^3H]muscimol binding) density, but no changes in cannabinoid receptors, in the STG of schizophrenia (Deng and Huang, 2005, 2006; Deng et al., 2007). Combining our data on binding densities of 5-HT_{2A}, muscarinic M1 and M2/M4, and GABA_A receptors from the same cohort of (both schizophrenic and control) subjects, there is a clear tendency for a positive correlation between 5-HT_{2A} and muscarinic M1 receptor bindings ($r = 0.44$, $p = 0.087$, Fig. 2A), and negative correlations between 5-HT_{2A} and GABA_A receptor bindings ($r = -0.44$, $p = 0.087$, Fig. 2B) and between muscarinic M1 and GABA_A receptor bindings ($r = -0.49$, $p = 0.057$, Fig. 2C).

4. Discussion

In this study, using [^3H]ketanserin we found a significant decrease in the binding density of 5-HT_{2A} receptors in the STG of the schizophrenia patients compared to the control subjects. In accordance with this study, a reduced expression of 5-HT_{2A} receptor mRNA has also been found in the STG in schizophrenia in a previous study (Burnet et al., 1996). This is the first study to examine binding density of 5-HT_{2C} receptors in human

postmortem brain tissue. There has also been no report on the expression of 5-HT_{2C} receptor mRNA in human postmortem brain tissue. These results suggest that the alterations of the 5-HT_{2A} receptors contribute to the pathophysiology of schizophrenia in the STG.

In line with our present findings, significant decreases in the density of [³H]ketanserin binding to the 5-HT_{2A} receptor have been reported in the prefrontal cortex and hippocampus (Burnet et al., 1996; Dean and Hayes, 1996; Scarr et al., 2004; Matsumoto et al., 2005). Only one previous study examined [³H]ketanserin binding in the STG and did not find any change in 5-HT_{2A} receptor density in schizophrenia, although decreases of 5-HT_{2A} receptor mRNA expression were observed in the same study (Burnet et al., 1996). It was not clear why Burnet et al. (1996) were not able to reveal the alteration of 5-HT_{2A} receptor density in the STG in schizophrenia.

We realized the reality that it is very difficult to completely exclude the effects of medication on the results using postmortem tissue. In fact, all schizophrenia subjects had chronic illness history with antipsychotic medication, in which they normally used more than one (often both typical and atypical) antipsychotic drugs during medication history. Therefore, it is difficult to differentiate the effects of different antipsychotics on receptor binding in postmortem studies. Previous work has shown that chronic treatment with the antipsychotic drug haloperidol does not affect [³H]ketanserin binding in rats (Burnet et al., 1996). However, atypical antipsychotics have a high affinity to 5-HT_{2A} receptors (for example: clozapine Ki=16 nM; olanzapine Ki=4 nM; risperidone Ki=0.5 nM) and 5-HT_{2C}

receptors (clozapine $K_i=16$ nM; olanzapine $K_i=23$ nM; risperidone $K_i= 25$ nM) (DeLeon et al., 2004). It has been reported that chronic treatment of 5-HT_{2A} antagonists can lead to a down-regulation of 5-HT_{2A} receptors in animal studies (Van Oekelen et al., 2003). Previously, we have also found that chronic olanzapine treatment reduces 5-HT_{2A} mRNA expression in rat brain at 2 hours after the last treatment, however, a rebound effect has been observed after 48 hours of drug withdrawal (Huang et al., 2006). This phenomenon may represent a rebound response in receptor production at the gene transcription level, which suggests that chronic treatment with antipsychotics (at least olanzapine) may not cause permanent alteration of 5-HT_{2A} receptor mRNA expression. It worth noting that an increase of 5-HT_{2A} binding in the caudate nucleus was observed in neuroleptic-naïve first episode schizophrenia, although there were no changes in cortical 5-HT_{2A} receptor binding in same subject (Erritzoe et al., 2008), which suggests that some changes in 5-HT_{2A} binding possibly occurs even without antipsychotic treatment.

Since the STG is involved in the pathology of schizophrenia, particularly in auditory hallucinations (Silbersweig et al., 1995; Kim et al., 2003; Gaser et al., 2004), abnormal transmission on 5-HT_{2A} receptors may contribute to auditory hallucinations in schizophrenia. In fact, there is an association between polymorphism of the 5-HT_{2A} receptor gene and hallucinations in schizophrenia (Ott et al., 2005). Since there is a clear tendency for a positive correlation between 5-HT_{2A} and muscarinic M1 receptor bindings, and negative correlations between 5-HT_{2A} and GABA_A receptor bindings and between muscarinic M1 and GABA_A receptor bindings, one possible mechanism of auditory hallucinations may be through interaction between 5-HT_{2A}, acetylcholine (ACh)

muscarinic and GABA transmissions. Previously, Dean has proposed a role for 5-HT/ACh muscarinic/GABA interactions in the pathology of the prefrontal cortex in schizophrenia, however he failed to find any correlations between 5-HT_{2A}, M1 and GABA_A receptors in the prefrontal cortex (Dean, 2001). 5-HT_{2A} receptors have been found to be located pre-synaptically on neurons innervating cholinergic terminals in the cortex and modulate Ach release (Morilak et al., 1993; Cassel and Jeltsch, 1995). Since cortical GABAergic interneurons express both 5-HT_{2A} and muscarinic receptors, these receptors may mediate inhibition of GABA release (Morilak et al., 1993; Hashimoto et al., 1994; Van der Zee and Luiten, 1999). Therefore, further studies on the interaction between 5-HT_{2A}, muscarinic and GABA receptors are necessary for a better understanding of the STG pathology of schizophrenia.

5. Conclusion

This study revealed a strong [³H]ketanserin binding in the STG, but only a very weak [³H]mesulergine binding in the STG. A significant decrease in binding of [³H]ketanserin was clearly observed in schizophrenia patients in comparison with control subjects. These results suggested that the alterations of the 5-HT_{2A} receptors contribute to pathophysiology of the STG in schizophrenia. Furthermore, there is a clear tendency for a positive correlation between 5-HT_{2A} and muscarinic M1 receptor bindings, and for negative correlations between 5-HT_{2A} and GABA_A receptor bindings and between muscarinic M1 and GABA_A receptor bindings. This provides a possible mechanism of auditory hallucinations through interactions between 5-HT_{2A}, acetylcholine muscarinic and GABA transmissions in the STG in schizophrenia.

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Table 1
Demographic and clinic data of schizophrenia subjects and controls

Subject no.	Age (years)	pH	PMI (h)	FRD	SUBS	Subtype diagnosis	Cause of death	Medication at death
<i>Schizophrenia (SZ)</i>								
1	51	6.02	21	400	No	Chronic residual	Ischaemic heart disease	Thioridazine, mesoridazine
2	27	6.25	27 (21–33)	314	Yes	Chronic paranoid	Hanging	Nil
3	67	6.36	5	1300	No	Chronic undifferentiated	Ischaemic heart disease	Thioridazine, risperidone
4	57	6.35	35.5 (33–38)	275	No	Chronic paranoid	Myocardial scarring	Thioridazine, sertraline
5	27	6.22	30	198	Yes	Chronic undifferentiated	Myocarditis	Clozapine
6	27	6.17	9.5 (9–10)	649	Yes	Chronic undifferentiated	Clozapine toxicity	Clozapine
7	30	6.60	24	325	No	Paranoid	Carbon monoxide poisoning	Clozapine
8	44	6.55	35 (27–43)	500	Yes D	Chronic undifferentiated	Hanging	Nil
Mean ± SE	43.5 ± 5.2	6.31 ± 0.07	19.9 ± 2.6	495 ± 354				
<i>Control</i>								
9	55	N/A	20				Cardiac arrest	Nil
10	37	N/A	21				Ischaemic heart disease	Nil
11	60	N/A	13				Acute myocardial	Nil
12	61	6.52	24				Ischaemic heart disease	Nil
13	18	6.10	33				Hypertrophic	Nil
14	37	5.25	11				Plumonary embolism	Nil
15	37	6.37	24				Electrocution	Nil
16	43	6.43	13				Thrombotic coronary artery occlusion	Nil
Mean ± SE	41.3 ± 5.6	6.13 ± 0.23	23.4 ± 4.0					
<i>P</i> (SZ vs Control; 2 tailed <i>t</i> -test)	0.77	0.47	0.38					

Abbreviation: PMI, postmortem interval; FRD, final recorded antipsychotic drug use (chlorpromazine equivalents per day); SUBS, substance users; D, Δ^9 -tetrahydrocannabinol detected in urine and blood at postmortem (Adopted from Deng C. & Huang X.-F., *Journal of Neuroscience Research*, 81:883–890. ©2005, with permission from John Wiley & Sons).

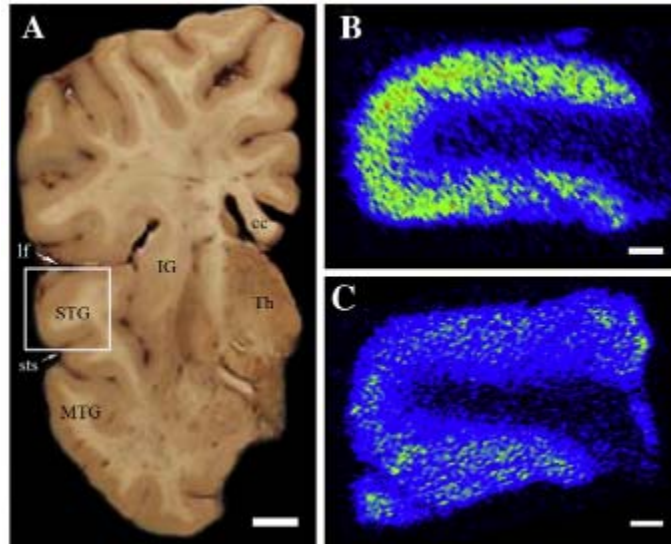


Figure 1 Examples of digital autoradiograms obtained with a Beta Imager to show [^3H]ketanserin bindings. (A) An example of postmortem brain tissue block to show the superior temporal gyrus (STG; enclosed in white lines) area used in this study; (B) [^3H]ketanserin binding in the STG of control subject; (C) [^3H]ketanserin binding in the STG of schizophrenia subject. Scale bars: 10 mm for A, and 2 mm for B and C. Abbreviations: cc, corpus callosum; IG, insular gyrus; If, lateral fissure; MTG, medial temporal gyrus; sts, superior temporal sulcus; Th, thalamus.

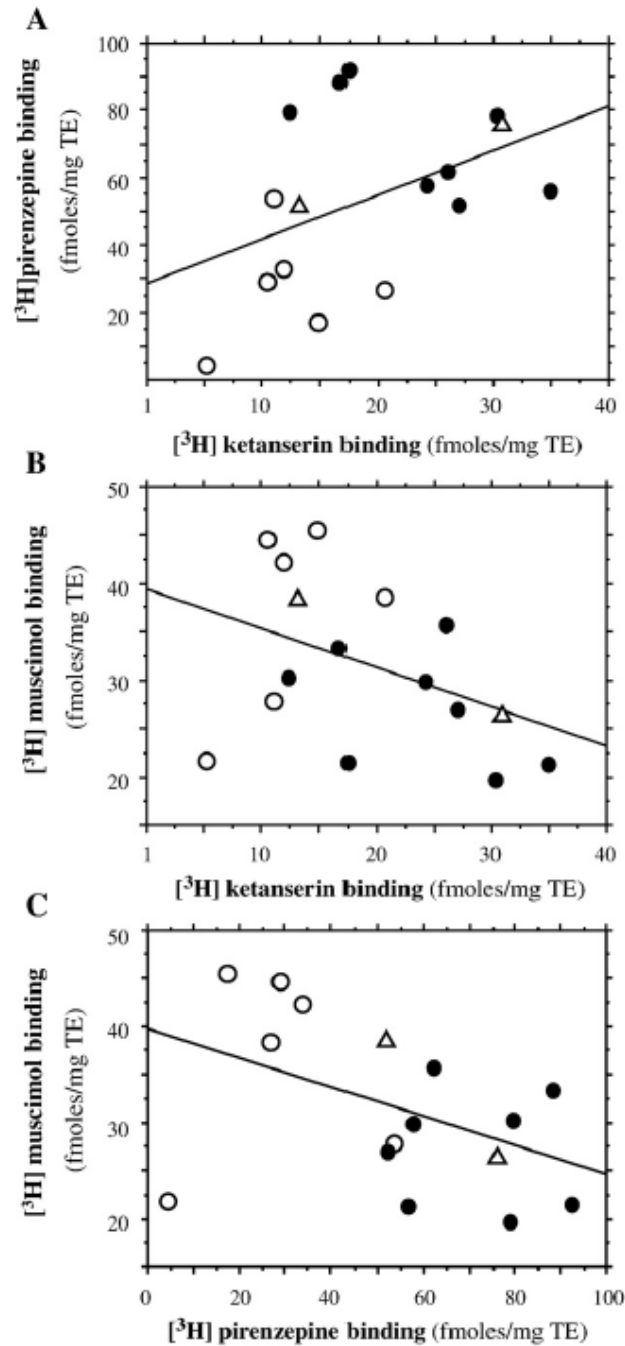


Figure 2 A, Correlation between the [³H]ketanserin and [³H]pirenzepine bindings in the STG ($r=0.44$, $p=0.087$). B, Correlation between the [³H]ketanserin and [³H]muscimol binding in the STG ($r=-0.44$, $p=0.087$). C, Correlation between the [³H]pirenzepine and [³H]muscimol binding in the STG ($r=-0.49$, $p=0.057$). The solid cycles represent the control subjects; the empty cycles are schizophrenic subjects with antipsychotic at death (Table 1); and the triangles are schizophrenic subjects without medication at death.