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# Understanding the neurotransmitter pathology of schizophrenia: selective deficits of subtypes of cortical GABAergic neurons

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**Summary.** Research aimed at understanding the neurotransmitter pathology of schizophrenia has been underway for half a century, with much emphasis on the dopamine system. Although this approach has advanced our understanding of treatment mechanisms, identification of primary dopaminergic abnormalities in the disease has been elusive. The increasing emphasis on a neuronal pathology of schizophrenia has led to the identification of abnormalities in GABAergic and glutamatergic systems; and we have identified selective deficits in GABAergic interneurons containing the calcium binding proteins parvalbumin and calbindin. Here we report further evidence for a loss of parvalbumin-immunoreactive neurons in both dorsolateral prefrontal and medial temporal cortex, indicating that these deficits are consistent with a subtle neurodevelopmental pathogenesis and hypothesising that they may contribute to a further degenerative process in schizophrenia.

**Keywords:** Schizophrenia, GABA, calcium binding proteins, cerebral cortex, human brain.

## Introduction

The essential neurotransmitter pathology of schizophrenia remains ill-defined, despite huge advances over the past half-century in identifying neurochemical and pathological abnormalities of the brain in this disease. From hypotheses in the early 1950's relating to aberrant transmethylation processes and disturbed serotonin transmission, the past decade has seen an increasing focus on dysfunctions in glutamate and/or GABA systems. But it has been the dopamine hypothesis that has provided much of the momentum for neurochemical research in schizophrenia, although it has contributed little

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to understanding the primary brain abnormality, as opposed to treatment mechanisms, in the disease.

The work of this research group has, for two decades, concentrated on understanding the neurotransmitter pathology and neurochemical pharmacology of schizophrenia and its treatment. Central to this research has been the use of human brain tissue collected at post mortem, an approach that was first introduced to us in Peter Riederer's laboratory in Vienna. Those initial studies (Reynolds et al., 1980, 1981) demonstrated that the increase in dopamine D2 receptors in the brain in schizophrenia (Owen et al., 1978) was most likely to be related to prior antipsychotic drug treatment, rather than to the disease process, as had previously been postulated. Although subsequent studies did identify a selective and specific lateralised amygdalar abnormality of dopamine itself (Reynolds, 1983), the emerging evidence for genuine, if subtle, cellular deficits in schizophrenia suggested that any dopaminergic abnormalities might be secondary to a neuronal pathology. A search for neurochemical indicators of deficient limbic innervation in the disease led to the finding of reductions in a GABA transporter in the hippocampus, itself related to the increases in (left hemisphere) amygdalar dopamine (Reynolds et al., 1990). This indicated a deficit in GABAergic innervation that provided a link between dopaminergic dysfunction and neuronal pathology.

Some of the most valuable pathological studies indicating neuronal deficits in schizophrenia have come from Benes and colleagues, who have consistent evidence for diminished numbers of GABAergic interneurons in the cortex (Benes et al., 1986, 1991). Their findings, along with those from several other groups, indicate that the GABAergic cells are not equally affected; there are selective deficits of subtypes of these interneurons (reviewed in Reynolds et al., 2001). Our recent approach to this has been to investigate the GABAergic subtypes defined by the presence of different calcium binding proteins (CBPs). Calretinin, calbindin and parvalbumin are neuroprotective CBPs that identify essentially non-overlapping subgroups of GABAergic neurons. Of these, parvalbumin is notable not only in its presence in functionally and morphologically distinct interneurons inhibiting the corticofugal pyramidal cells, but in being expressed relatively late during development, after synaptic contacts have been established (Solbach and Celio, 1991), appearing several months post-natally in humans (Reynolds and Beasley, 2001). Calbindin expression is also incomplete at birth in humans, with further expression and rearrangement in the early months, while the pattern of calretinin expression is well-established before birth.

Our initial studies demonstrated that parvalbumin-immunoreactive GABAergic interneurons were significantly diminished in the frontal cortex in schizophrenia (Beasley and Reynolds, 1997), while calretinin-containing cells were unaffected (Reynolds and Beasley, 2001). This finding provided support for our hypothesis that the late expression of parvalbumin may impart a period of vulnerability to this subgroup of GABAergic neurons, which would then be selectively sensitive to potentially toxic events during development. This hypothesis provides a much needed link between the evidence for

schizophrenia as a disorder of neurodevelopment and the selective GABAergic pathology of the disease.

We have recently confirmed our original findings in a further series of frontal cortical (Brodmann area 9) brain tissue from psychiatric and control subjects (Beasley et al., 2002), demonstrating too that there was some deficit in calbindin-, as well as parvalbumin-immunoreactive neurons in schizophrenia. We also observed a similar trend to such interneuronal deficits in bipolar disorder, suggesting that the selective pathology might generalise to patients with psychotic disorder. Further study in hippocampal tissue (Zhang and Reynolds, 2002) identified a far more profound deficit of over 50% in parvalbumin-immunoreactive neurons in schizophrenia, again in the absence of any calretinin deficit.

We have gone on to study two further regions of the cerebral cortex to assess their GABAergic neuronal deficits by quantitative assessment of CBP-immunoreactivity. One of these regions, the dorsolateral prefrontal cortex (area 46) is strongly implicated in negative and cognitive deficits in schizophrenia (e.g. Bunney and Bunney, 2000). The other, the entorhinal cortex, has close functional links to the hippocampus, and has also been reported, although not always consistently, to demonstrate histological abnormalities in the disease (Arnold et al., 1991; Arnold, 1997; Krimer et al., 1997).

## Methods and materials

### *Human subjects*

Samples were obtained from the Stanley Foundation Neuropathology Consortium brain collection. Brains were obtained from patients diagnosed with schizophrenia, bipolar disorder, major depressive disorder and from matched controls (15 from each group). Demographic details are described in Torrey et al. (2000). Final diagnoses were established using DSM-IV criteria and routine microscopical and toxicological examinations carried out on all cases.

### *Immunocytochemistry*

10 μm thick paraffin sections of the entorhinal and dorsolateral prefrontal (area 46) cortices were processed for parvalbumin-, calbindin- (only in area 46) or calretinin-immunoreactivity randomly and blind to diagnosis. For each antibody two sections were sampled for analysis. Tissue sections were microwaved for 30 minutes in 0.05 M tris buffer, pH 9.0 to aid antigen retrieval. Sections were blocked, then incubated for 36 hours at 4°C with a mouse monoclonal antibody against parvalbumin (clone PA-235, Sigma, St Louis, MO), a mouse monoclonal antibody against calbindin (Sigma) or a goat polyclonal antibody against calretinin (Swant, Bellinzona, Switzerland), each at a dilution of 1:5,000. Following this the sections were processed by the avidin-biotin method of using a Vectastain ABC kit (Vector Laboratories, Burlingame, CA). Peroxidase was visualised using diaminobenzidine (DAB), intensified with nickel chloride, and sections counterstained with toluidine blue. Negative control sections, in which the primary antibody was omitted from the staining protocol, were run alongside the test series.

### *Image analysis*

The boundaries of Brodmann area 46 were determined according to the criteria of Rajkowska and Goldmann-Rakic (1995) and Daviss and Lewis (1995) and those of the

intermediate entorhinal cortex according to Beall and Lewis (1992). Parvalbumin-, calbindin- and calretinin-immunoreactive neurons were plotted at 100x magnification using an Olympus microscope equipped with camera lucida. The density of neuronal profiles was expressed as mean values (± standard errors) per $mm^2$ per cortical layer from a total of ten 500 μm wide cortical traverses, each from the pial surface to the white matter border. Cortical width was also measured for each of these traverses.

### *Statistical analysis*

The mean total cortical densities of each cell population was compared between the schizophrenic and control groups using univariate analysis of variance (ANOVA). Demographic and histological variables including age, sex, post-mortem interval, brain hemisphere, brain pH and time in fixative were considered to be confounders, and therefore included in the analysis as covariates, if they differed between the schizophrenic group and the control group at the 10% significance level (ANOVA) and could also be shown empirically to predict densities at the 10% significance level (ANOVA or Spearman's Rank Correlation). Following this analysis the mean density of parvalbumin-, calbindin- (for area 46), and calretinin-immunoreactive neurons in each cortical layer for each of the three patient groups was compared with that of the control group in each region. This allowed us to look for disease and laminar specificity. Mean densities were analysed by univariate ANOVA using diagnoses as contrasts. In order to account for multiple layer-wise testing, p-values of 0.010 (for calbindin and calretinin in area 46) and 0.013 (for parvalbumin in area 46 and calretinin in entorhinal cortex) and 0.017 (for parvalbumin in entorhinal cortex) were determined to be statistically significant; these values represent the 5% level divided by the number of layers analysed. All statistical analysis was carried out in SPSS 10.

## Results

CBP-immunoreactive interneurons in the cortex were generally intensely stained and easy to distinguish. Both parvalbumin- and calretinin-immunoreactive cells demonstrated a substantially higher density in the dorsolateral prefrontal region than in the entorhinal cortex (Table 1). At the 10% level mean fixation time ($p = 0.011$) and mean postmortem interval ($p = 0.038$) was significantly higher for the schizophrenic group than for the controls. However, Spearman's rank correlation indicated no significant correlation between these variables and the density of any neuronal population at the 10%

**Table 1.** Total cortical densities of CBP-immunoreactive neurons

| | Schizophrenia | Bipolar disorder | Depression | Control |
|---|---|---|---|---|
| *Dorsolateral prefrontal cortex (BA 46)* | | | | |
| Parvalbumin | 21.8 ± 2.3* | 23.9 ± 2.7 | 26.4 ± 1.9 | 28.8 ± 2.0 |
| Calbindin | 22.0 ± 2.2 | 22.9 ± 1.8 | 26.8 ± 1.4 | 27.6 ± 1.9 |
| Calretinin | 39.1 ± 2.7 | 39.8 ± 3.4 | 37.8 ± 1.9 | 43.2 ± 1.9 |
| *Entorhinal cortex* | | | | |
| Parvalbumin | 6.1 ± 0.6* | 7.4 ± 1.3 | 7.6 ± 0.8 | 9.0 ± 1.1 |
| Calretinin | 13.5 ± 1.3 | 14.9 ± 1.3 | 12.9 ± 1.4 | 14.5 ± 1.3 |

Data expressed as mean ($cells.mm^{-2}$) ± s.e.m.; *$p < 0.05$ vs. controls

**Table 2.** The relative laminar density of calcium binding protein-immunoreactive neurons in the dorsolateral prefrontal cortex (BA 46)

| | Diagnosis | | | | |
|---|---|---|---|---|---|
| | Cortical layer | Schizophrenia | Bipolar disorder | Depression | Control |
| Parvalbumin | I | 0 | 0 | 0 | 0 |
| | II | 9.7 ± 1.7 | 10.9 ± 2.2 | 12.4 ± 2.8 | 13.9 ± 2.1 |
| | III | 29.5 ± 3.3 | 32.3 ± 4.3 | 34.4 ± 2.5 | 39.6 ± 2.8 |
| | IV | 61.5 ± 6.6 | 60.4 ± 5.9 | 64.5 ± 3.0 | 68.0 ± 5.4 |
| | V/VI | 13.0 ± 1.6 | 15.3 ± 2.0 | 18.7 ± 2.5 | 18.6 ± 2.0 |
| Calbindin | I | 2.3 ± 0.6 | 2.4 ± 0.7 | 3.4 ± 0.5 | 2.8 ± 0.5 |
| | II | 110.6 ± 8.9 | 104.9 ± 7.9 | 123.1 ± 6.0 | 126.0 ± 8.9 |
| | III | 22.4 ± 3.2 | 23.8 ± 2.4 | 28.7 ± 1.9 | 30.2 ± 2.9 |
| | IV | 8.1 ± 1.8 | 8.6 ± 1.2 | 11.4 ± 1.8 | 12.0 ± 1.9 |
| | V/VI | 9.4 ± 1.0 | 10.7 ± 1.1 | 10.3 ± 1.1 | 9.6 ± 0.8 |
| Calretinin | I | 55.1 ± 4.6 | 53.2 ± 5.1 | 42.7 ± 3.4 | 57.9 ± 5.0 |
| | II | 126.3 ± 9.6 | 125.0 ± 9.9 | 115.8 ± 7.7 | 132.4 ± 7.1 |
| | III | 45.8 ± 3.0 | 47.8 ± 3.2 | 46.1 ± 1.9 | 49.6 ± 2.1 |
| | IV | 26.5 ± 2.5 | 25.6 ± 2.7 | 25.0 ± 2.0 | 26.4 ± 2.0 |
| | V/VI | 7.3 ± 0.6 | 8.4 ± 0.8 | 8.1 ± 0.6 | 9.2 ± 0.7 |

Data expressed as mean (cells.mm$^{-2}$) ± s.e.m.

level and so group comparisons were not adjusted for these variables. Although significant correlations were observed in area 46 between tissue pH and parvalbumin and calbindin neuronal density and, interestingly, between age and parvalbumin neuronal density ($p = 0.013$, $r = 0.449$), neither tissue pH nor age differed between the schizophrenic and control groups.

Summaries of mean densities for each neuronal subpopulation are shown in Table 1. In area 46, significant reductions ($p = 0.029$) in the total cortical density of parvalbumin-containing cells were observed in the schizophrenic group. The density of calbindin-containing neurons was also reduced but was not statistically significant ($p = 0.070$), while the density of calretinin-immunoreactive cells did not differ between the two groups. The same pattern was seen in entorhinal cortex, where the reduction in parvalbumin-immunoreactive cells was also significant ($p = 0.026$), with no difference for calretinin.

To look for disease and laminar specificity the mean density of parvalbumin-, calbindin-, and calretinin-immunoreactive neurons in each cortical layer for each of the three patient groups were compared with that of the control group (Tables 2 and 3). As described for schizophrenia, mean fixation times for bipolar disorder ($p = 0.001$) and major depression ($p = 0.055$) and mean postmortem intervals for bipolar disorder ($p = 0.085$) were higher than for controls. However, Spearman's rank correlation indicated no significant correlation between these variables and the density of any neuronal population at the 10% level, except for calretinin neuronal density in the entorhinal

**Table 3.** The relative laminar density of calcium binding protein-immunoreactive neurons in the intermediate entorhinal subdivision of the entorhinal cortex

| | Diagnosis | | | | |
|---|---|---|---|---|---|
| | Cortical layer | Schizophrenia | Bipolar disorder | Depression | Control |
| Parvalbumin | I | 0 | 0 | 0 | 0 |
| | II | 7.4 ± 1.2 | 8.3 ± 1.3 | 5.5 ± 0.9 | 12.2 ± 2.7 |
| | III | 10.3 ± 1.0* | 14.7 ± 2.7 | 13.0 ± 1.4 | 15.1 ± 1.6 |
| | V/VI | 3.4 ± 0.5 | 3.5 ± 0.7 | 4.7 ± 0.7 | 4.7 ± 0.7 |
| Calretinin | I | 13.1 ± 2.0 | 15.1 ± 3.0 | 9.3 ± 2.3 | 14.0 ± 3.8 |
| | II | 29.5 ± 4.1 | 33.0 ± 3.1 | 23.9 ± 3.5 | 27.5 ± 4.4 |
| | III | 11.8 ± 1.5 | 16.0 ± 2.0 | 12.8 ± 1.2 | 13.8 ± 1.1 |
| | V/VI | 10.4 ± 1.3 | 9.0 ± 1.1 | 10.9 ± 1.4 | 11.7 ± 0.7 |

Data expressed as mean (cells.mm$^{-2}$) ± s.e.m.; * $p < 0.05$ vs. controls after correction for multiple testing

cortex, which correlated with mean fixation time ($r = 0.280$, $p = 0.032$). This variable was included as a covariate in the analysis.

In area 46, significant correlations were observed between tissue pH and parvalbumin ($p = 0.001$, $r = 0.522$) and calbindin ($p = 0.001$, $r = 0.419$) neuronal density and between age and parvalbumin neuronal density ($p = 0.001$, $r = 0.405$). In the entorhinal cortex, no significant correlation was found between any potentially confounding variable and parvalbumin neuronal density.

In area 46 significant reductions in the density of parvalbumin-immunoreactive neurons were observed in cortical layer III ($p = 0.032$) and cortical layer V ($p = 0.048$) in the schizophrenic group compared with the control group. The density of calbindin-immunoreactive neurons was reduced in layer III in the schizophrenic group compared with controls. The density of calretinin-immunoreactive neurons was reduced in cortical layer I in the major depressive disorder group ($p = 0.020$) and in cortical layer V in the schizophrenic group ($p = 0.037$), compared with controls. However, using the stricter criteria to account for multiple comparisons, none of the reductions attained statistical significance. In the entorhinal cortex only calretinin neuronal density in layer V/VI in the bipolar group reached the 5% level below control values ($p = 0.041$). Parvalbumin neuronal density showed an effect in layer II in depression ($p = 0.026$) and in layer III in schizophrenia ($p = 0.017$). Of these results only the latter attains statistical significance using the stricter criteria.

No significant gender by diagnosis or side by diagnosis interactions were noted for any neuronal subpopulation. In the schizophrenic and bipolar disorder groups no significant correlations were noted between any neuronal subpopulation and lifetime antipsychotic dose. Cortical width in either region did not differ between groups.

## Discussion

These results provide further support for a cortical deficit in parvalbumin-immunoreactive GABAergic neurons in schizophrenia that extends not only to several areas of the prefrontal cortex and to the hippocampus, but also to the entorhinal cortex. The deficit in this latter region, at 68% control density, is slightly greater than that in the frontal cortex, but not as profound as the deficits found in the hippocampus (Zhang et al., 2002). Due to the paucity of staining in the medial temporal lobe, calbindin-immunoreactive neurons were not determined in the entorhinal cortex. However the tendency to a lower density of these cells in area 46 in schizophrenia was consistent with our observations in area 9 in the same cases (Beasley et al., 2002). The absence of any significant decreases in calretinin-immunoreactive cells further underlines the specificity of the interneuronal deficit in schizophrenia.

These data are certainly consistent with our hypothesis that the late expression of parvalbumin, and perhaps calbindin, may result in a window of vulnerability of this subgroup of GABAergic neurons during development, and that various potential traumata during pre- and/or early postnatal life could result in a loss of these cells. However, it is conceivable that these interneurons are not lost but merely no longer expressing the CBP. Such a loss of expression in otherwise viable neurons could relate to an aetiological factor, be a consequence of the disease pathology, or be an artifactual effect associated with, say, drug treatment. There is no support for the latter explanation, since preliminary studies suggest parvalbumin expression is increased following antipsychotic drug treatment (Scruggs and Deutch, 1999). Nevetheless it is not possible to rule out differential effects of different drug treatments on CBP expression following chronic treatment in humans. There are indications that some GABAergic neuronal function is lost in the absence of any deficit of cortical neurons (Akbarian et al., 1995), although the methods used may not have the resolution to identify a small reduction within a subgroup of neurons.

Whether the interneurons are lost or just less active, treatment that increases their activity in schizophrenia should tend to restore normal function. Thus it is notable that the parvalbumin-containing interneurons selectively receive a dopaminergic innervation (Sesack et al., 1998); investigation of other receptor sites found selectively on parvalbumin- and/or calbindin-immunoreactive GABAergic neurons may provide novel targets for antipsychotic drug development.

The GABAergic deficit that we observe provides further support for a recent hypothesis proposed to explain other neuropathological aspects of schizophrenia and the progressive cognitive deficits that occur in the disease. The NMDA receptor hypofunction hypothesis (Olney and Farber, 1995) draws on the observation that drugs that block the glutamate/NMDA receptor, such as phencyclidine (PCP), are not only effective in modelling both the positive and negative symptoms of schizophrenia (Javitt and Zukin, 1991), they can also induce a specific pattern of neuronal damage. This damage occurs in adult animals, and is proposed as a mechanism underlying the late

onset neurodegenerative changes and cognitive deterioration seen in cases of schizophrenia. Notable in the context of the current data is that this damage due to NMDA receptor blockade is mediated by a hypofunction of GABAergic neurons (Olney and Farber, 1995), presumably reflecting antagonism of NMDA receptors on these cells. Thus the selective deficit in GABAergic neurons, that normally provide inhibitory control of the cortical pyramidal cells, may be responsible for subsequent damage to this glutamatergic pathway. Certainly we and others have found evidence of glutamatergic deficits in cortical and corticostriatal innervation (e.g. Deakin et al., 1989; Aparicio-Legarza et al., 1997; Nudmamud and Reynolds, 2001).

These observations provide a two-stage model of the pathogenesis of schizophrenia whereby early developmental GABAergic losses eventually result in a progressive process of further, glutamatergic deficits. Although speculative, this hypothesis lends itself to testing in animals and could provide a disease model of improved construct validity.

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