Evidence for Decreased DARPP-32 in the Prefrontal Cortex of Patients With Schizophrenia

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Background: The neurotransmitters dopamine and glutamate have been implicated in the prefrontal dysfunction associated with schizophrenic illness. Studies suggest that the D1 subclass of dopamine receptor and the N-methyl-D-aspartate subclass of glutamate receptor are involved in this prefrontal dysfunction. These 2 receptors regulate, in opposing directions, the amount of phosphorylated activated DARPP-32, a potent inhibitor of protein phosphatase 1 that modulates the activity of several classes of receptors and ion channels. Thus, DARPP-32 occupies a key regulatory position, and may play an important role in the pathophysiological changes in dopamine and glutamate function reported in patients with schizophrenia.

Methods: The amounts of DARPP-32, synapsin I, and the α subunit of calcium/calmodulin-dependent protein kinase II were measured by immunoblotting in postmortem samples from 14 schizophrenic subjects and their age-, gender-, and autolysis time–matched control subjects. Possible confounding influences of neuroleptic treatment were analyzed by comparing subjects with Alzheimer disease who were and were not treated with neuroleptic agents.

Results: DARPP-32 was significantly reduced in the dorsolateral prefrontal cortex in more schizophrenic subjects relative to matched controls. The ratios of 2 other synaptic phosphoproteins, synapsin I and the α subunit of calcium/calmodulin-dependent protein kinase II, did not differ between schizophrenic and control subjects, nor between subjects with Alzheimer disease who were and were not treated with neuroleptic agents.

Conclusions: Our findings are consistent with a selective reduction in DARPP-32 levels in schizophrenic subjects. This may be involved in the prefrontal dysfunction associated with schizophrenia.

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DARPP-32 is specifically localized to neurons containing dopamine receptors. It is a potent inhibitor of protein phosphatase 1, which plays a central role in dopaminergic and glutamatergic signaling and in integrating the activity of these 2 pathways (Figure 1). (Greengard et al provide a review.) Dopamine, through a pathway involving D1 receptor activation of cyclic adenosine monophosphate–dependent protein kinase, stimulates the phosphorylation of DARPP-32. Dopamine, through activation of the D2 receptor, and glutamate, through activation of the N-methyl-D-aspartate (NMDA) glutamate receptor, increase the activity of calcineurin, which results in the dephosphorylation of DARPP-32. In its phosphorylated, but not dephosphorylated, state, DARPP-32 potently inhibits the major serine/threonine protein phosphatase 1. Through its inhibition of protein phosphatase 1, DARPP-32 controls the state of phosphorylation and the physiological activity of several key proteins, including ion channels, ion pumps, neurotransmitter receptors, and transcription factors; thus, DARPP-32 controls the physiological characteristics of neurons containing dopamine receptors. The importance of DARPP-32 in the regulation of dopaminergic function is clearly demonstrated by the alterations in dopaminergic signaling evident in mice with a targeted deletion of DARPP-32.

Much evidence implicates abnormalities of dopaminergic and glutamatergic neurotransmission in the pathophysiological features of schizophrenia. Compounds that increase synaptic dopamine levels (eg, amphetamines and related compounds) induce or exacerbate psychotic behavior in a significant subgroup of schizophrenic, but not healthy, subjects, while dopamine receptor antagonists ameliorate symptoms. Similarly, noncompetitive NMDA receptor antagonists (eg, phencyclidine, ketamine, and dizocilpine) can induce prolonged psychotic episodes in schizophrenic subjects in contrast to short episodes in non-schizophrenic subjects. These findings provide pharmacological evidence compatible with altered dopaminergic and glutamatergic function in patients with schizophrenia.
MATERIALS AND METHODS

ACQUISITION, STORAGE, AND PREPARATION OF BRAIN TISSUE

Brain specimens of schizophrenic patients and control subjects, individually matched for age, gender, and autolysis time, as described in detail in Table 1, were used. Although patients were not matched for cause of death, no patients received mechanical ventilation before death. The matching process was finished before all experimental procedures were undertaken. The diagnosis of schizophrenia was made before and after the deaths of the schizophrenic patients and control subjects by 2 board-certified psychiatrists (S.G.P. and W.E.B.). Informed consent was obtained from the next of kin and, in one third of the cases, from the patients themselves before death. Diagnoses were made according to DSM-IV criteria by using the best-estimate diagnostic procedure from all available interview and medical record sources. These sources included interviews with the subjects and/or postmortem interviews with a family member, a significant other, and/or a treating professional. Exclusion criteria for the schizophrenic patients and control subjects included a history of neurological illnesses with the exception of neuroleptic-induced seizures; positive test results for the human immunodeficiency virus; neuropsychological evidence of stroke, Alzheimer disease (AD), brain tumor, or vascular anomalies; and a history, or evidence at autopsy, of severe drug abuse (eg, needle tracks or a positive toxicological profile for substances of abuse). Moderate marijuana or alcohol use or occasional recreational drug use were not exclusionary criteria, unless they confounded the Axis I diagnosis (eg, cocaine or amphetamine abuse resulting in psychosis). All schizophrenic patients had a long-term non-remitting pattern of illness. Neuroleptic drugs taken by the patients included butyrophenones, phenothiazines, and/or thioxanthenes. Atypical neuroleptic agents, such as benzamides (eg, sulpiride), dibenzepines (eg, clozapine), or risperidone, had not been taken by any of the schizophrenic patients. For religious reasons, schizophrenic patient 6 had taken no neuroleptic drugs for 10 years before death.

The second set of brain specimens was obtained from 9 patients with AD who were treated with haloperidol and 9 patients with AD who were not treated with any neuroleptic agents. They were matched for age and postmortem delay, as described in detail in Table 2. Postmortem delay, the time from death to autopsy, was listed in Table 2 rather than autolysis time, the time from death to freezing of the brain, because autolysis time was unavailable for the patients with AD. The patients with AD were included to determine whether differences observed in the schizophrenic cohort could be attributable to neuroleptic treatment. Patients with AD often receive lower doses of antipsychotic medication for shorter periods.

The brain specimens of the control subjects were obtained from the coroner’s office or the eye bank. The coroner’s office or eye bank investigators determined that there had been no psychiatric illness in the subjects based on the findings from their investigative review. The absence of a psychiatric illness was further confirmed by the results of a telephone interview with a family member, a review of available medical records, and/or consultation with the control subject’s family physician. Statistical analyses from previous studies identified no confounding influences of the matching variables.

Patients and controls were individually matched by using the following order and criteria: (1) gender; (2) age difference (mean difference, 5.0±4.9 years); (3) autolysis time of 3½ hours (mean time, 2.7±2.1 hours); and, if possible, (4) cause of death. For the schizophrenic group (n=14), the age was 38.3±21.5 years, the autolysis time was 15.8±10.5 hours, and the disease duration was 30.6±18.7 years. For the control group (n=14), the age was 61.5±22.3 years and the autolysis time was 15.9±10.3 hours. In each group of schizophrenic and control subjects, there were 4 women and 10 men. For the haloperidol-treated patients with AD (n=9), the age was 76.4±4.8 years, the postmortem delay was 5.0±2.4 hours, and the disease duration was 7.9±2.2 years. There were 5 women and 4 men. For the untreated patients with AD (n=9), the age was 73.9±12.0 years, the postmortem delay was 4.6±1.5 hours, and the disease duration was 10.0±5.4 years. There were 4 women and 5 men. (Data are given as mean±SD unless otherwise indicated.)

A computer program was used to identify potential control subjects as possible matches for patients in the schizophrenic cohort. The brain specimens of the control subjects were taken from a control brain repository that consisted of more than 100 cases. Of those cases identified by the computer, the composite records of the possible matches were carefully reviewed to satisfy criteria for schizophrenia and normality, following which the best matches were selected. Examination of the brain tissue by a board-certified neuropathologist excluded tumors and vascular and other abnormalities in the analyzed brain specimens.

Procedures for removal and storage of the brain specimens have been described previously. Briefly, each brain specimen was cut into coronal slices of about 0.9-cm thickness, and slices were flash frozen between 2 supercooled aluminum plates. In all sampling, tissue from each subject’s brain was processed together with tissue from the matched control brain. From the left side of each brain, several blocks of frozen gray matter (size, 2 cm²) were

RESULTS

DARPP-32 IN THE DLPFC OF SCHIZOPHRENIC VS CONTROL SUBJECTS

DARPP-32 protein levels were analyzed by immunoblotting in the DLPFC from 14 pairs of schizophrenic and individually matched control subjects. The present study
obtained from the DLPFC at the tip of the superior frontal gyrus, corresponding to the rostral part of Brodmann area 9. Blocks were first cut from coronal slices of about 0.9-cm thickness; extreme care was taken not to include any subcortical white matter that, if present, was trimmed off. The samples were coded, paired, and sent on dry ice to the processing laboratory. The investigators in the processing laboratory were blinded to the sample identities.

**IMMUNOBLOTTING**

Frozen samples (0.25-0.50 g of tissue) were homogenized in 20 volumes of boiling 1% wt/vol sodium dodecyl sulfate containing 1 µg/mL of leupeptin (Chemicon International, Inc, Temecula, Calif), sonicated, and boiled for 5 minutes. The samples were centrifuged at 1000g for 5 minutes; the protein concentration in the supernatants was determined by the bicinchoninic acid method (Pierce Biotechnology, Inc, Rockford, Ill). Protein (100 µg per lane) was subjected to 10% sodium dodecyl sulfate–polyacrylamide gel electrophoresis, as described. Samples from each pair of subjects and matched control samples were run in quadruplicate on the same gel to minimize variations in transfer and immunolabeling. The proteins were transferred to 0.2-µm nitrocellulose (Schleicher & Schuell Bioscience, Inc, Keene, NH) at 200 mA for 18 hours. After transfer of the proteins onto nitrocellulose, the gels were stained with Coomassie blue to visualize protein loading and transfer efficiency. If this assessment demonstrated protein degradation in any sample, the sample and its match were not included in the analysis. All blotting steps were performed at room temperature in blotting buffer (a combination of 86mM sodium phosphate, pH 7.3; 150mM sodium chloride; 0.05% vol/vol polyethylene sorbitol monolaurate [Tween 20]; [Sigma-Aldrich Corp, St Louis, Mo]; and 0.02% wt/vol sodium azide). Nonspecific binding was blocked by incubation in blotting buffer containing 2.3% wt/vol nonfat dry milk (Carnation) for 8 hours. After 2 rinses (15 minutes each), blots were cut into sections containing the proteins of interest. The blot sections were incubated for 2 hours with primary antibodies to DARPP-32 (mouse monoclonal antibody C24-6a, 1:1000 dilution), synapsin I (rabbit polyclonal antibody G-472 [1:200 dilution], G454/455 [1:2000 dilution], or G486 [1:2000 dilution]), or the α subunit of calcium/calmodulin-dependent protein kinase II (CaMK IIa) (rabbit polyclonal antibody RU16, 1:1000 dilution). None of the antibodies used was selective for the phosphorylation state of the proteins, ie, phosphorylated and dephosphorylated forms should be detected equally. After 2 rinses (15 minutes each), the DARPP-32 blot sections were incubated for 1 hour with rabbit anti–mouse IgG (1:500 dilution) (Pierce Biotechnology, Inc). After 2 rinses (15 minutes each), all blot sections were incubated for 90 minutes in iodine 125 labeled protein A (1:1000 dilution) (Amersham Holdings, Inc, Arlington Heights, Ill). After two 15-minute and two 5-minute rinses, the blot sections were dried, wrapped in plastic, and subjected to imaging analysis (PhosphorImager; Molecular Dynamics, Sunnyvale, Calif).

Multiple experiments were conducted. Within each experiment, 4 replicate lanes from each member of a matched pair were run together on a single gel to minimize variability between blots. The data were expressed in arbitrary units obtained from the imaging instrument (PhosphorImager), and a mean value of the 4 lanes for each experiment was calculated. For each pair, the ratios of the mean values from each experiment (schizophrenic/control subjects and haloperidol-treated/untreated subjects with AD) were computed; the mean of the ratios calculated for the matched pairs across experiments was the final value used for statistical comparisons.

**STATISTICAL ANALYSES**

Results were analyzed statistically by the binomial exact test, which was used to test the hypothesis that the ratio of matched data pairs came from a binomial population with a specified probability of an event. The binomial analysis was selected because of the assumption that each paired comparison (schizophrenic vs matched control) must be treated as a separate experiment as opposed to comparing the differences between the groups. This assumption is required because the absolute values for the immunoblotting procedures, although highly reliable within a pairwise comparison, are not comparable across experiments because of variability in transfer efficiency, immunolabeling efficiency, ²/²I-specific radioactivity, and imaging instrument (PhosphorImager) values, factors that cannot be completely controlled. Thus, absolute values from one pairwise comparison are independent from the same pairwise comparison at another time. The calculation of the pairwise ratio and the computation of means across experiments control for the inherent variability. Thus, the ratio across experiments (which summarizes the differences between the members of each pair) is a reliable estimate. The ratios were converted to dichotomous variables, with one category of values equal to or greater than 1 (ie, schizophrenic subjects have higher values than controls) and the second category of values less than 1 (ie, schizophrenic subjects have lower values than controls). With a cut point of 0.5, the null hypothesis that there was an equal chance that the ratio will sort into either of the 2 categories was tested. The binomial exact test in this case measures and tests the significance of the number of pairwise comparisons in which schizophrenic subjects have either higher or lower values than matched controls.
CaMK IIα AND SYNAPSIN I IN SCHIZOPHRENIC VS CONTROL SUBJECTS

For comparison with DARPP-32, the levels of 2 synaptic phosphoproteins, CaMK IIα and synapsin I, were analyzed by immunoblotting in the DLPFC from 14 pairs of schizophrenic and matched control subjects (Figure 3B and C, respectively). The ratios of CaMK IIα and synapsin I were not different between schizophrenic and control brain specimens. For synapsin I, there were 4 pairs in whom the ratio of the value in the schizophrenic subjects to that in the controls was less than 1, 6 pairs in whom this ratio was not different from 1, and 4 pairs in whom this ratio was greater than 1. For CaMK IIα, there were 3 pairs in whom the ratio of the value in the schizophrenic subjects to that in the control was less than 1, 10 pairs in whom this ratio was not significantly different from 1, and 1 pair in whom this ratio was greater than 1.

DARPP-32, CaMK IIα, AND SYNAPSIN I IN PATIENTS WITH AD

It is possible that the differences observed in the schizophrenic cohort could be attributable to neuroleptic treatment. To address the issue, we examined the effect of such treatment by comparing the relative amounts of...
DARPP-32, CaMK II, and synapsin I in 9 patients with AD who were treated with haloperidol with those in matched patients with AD who were not treated with neuroleptic agents (Figure 4). The ratios of each of these proteins in the DLPFC was not different (P > .05) for haloperidol-treated patients with AD vs untreated patients with AD. For DARPP-32, there were 4 pairs in whom the ratio of the value in the treated patient divided by the value in the control was less than 1, 1 pair in whom this ratio was not significantly different from 1, and 4 pairs in whom this ratio was greater than 1. For CaMK II, there were 3 pairs in whom this ratio was less than 1, 4 pairs in whom this ratio was not significantly different from 1, and 2 pairs in whom this ratio was greater than 1. For synapsin I, there were 3 pairs in whom this ratio was less than 1, 4 pairs in whom this ratio was not significantly different from 1, and 2 pairs in whom this ratio was greater than 1.

In all cases, the relative molecular mass values of DARPP-32, synapsin 1, and CaMK II were the same in all pairs (schizophrenic/control subjects and subjects with AD with/without haloperidol treatment) (data not shown). The relative molecular mass values of DARPP-32 (32 kd) and synapsin 1 (a doublet of 86 and 80 kd) were previously reported to be the same in the postmortem human brain as in the rat brain.26 The relative molecular mass value of CaMK II in our human samples was 50 kd, the same as in the rat brain.27

Figure 1. Central role of DARPP-32 as a molecular integrator of dopaminergic and glutamatergic signaling. Multiple first messengers acting through the second messengers cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), and calcium (Ca2+) regulate the phosphorylation of DARPP-32 at threonine 34, which in its phosphorylated form (pDARPP-32) inhibits protein phosphatase 1 (PP-1). Phosphorylation of threonine 34 is regulated through protein kinase A (PKA) and protein kinase G (PKG) by various transmitters, principally by dopamine acting at D1 receptors. DARPP-32 phosphorylated at threonine 34 is dephosphorylated by protein phosphatase 2B (PP-2B) (also known as calcineurin), a Ca2+/calmodulin-dependent phosphatase, which is activated by several transmitters, principally following Ca2+ influx produced by glutamate acting at N-methyl-D-aspartate (NMDA) and L-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. The psychostimulants cocaine and amphetamine increase DARPP-32 phosphorylation by increasing dopaminergic transmission. Neuroleptic drugs achieve certain of their clinical effects by antagonism of dopamine D2 receptors, an action that leads to an increase in DARPP-32 phosphorylation indirectly by reducing the intracellular Ca2+ concentration. Through the regulation of PP-1 activity, which has a broad substrate specificity, various first messengers are able to modulate the function of receptors (NMDA, AMPA, γ-aminobutyric acid A [GABA_A], and neurokinin A [NKA]), ion channels (L-, N-, and P-type Ca2+ channels; and sodium [Na+] channels), and transcription factors (cAMP response element binding protein [pCREB] and fos-related antigens [FRAs]). CCK indicates cholecystokinin; A2A, adenosine 2A; 5HT4, serotonin 4; VIP, vasoactive intestinal polypeptide; NO, nitric oxide; and p, phosphorylated.
This study demonstrates that the protein level of DARPP-32 is decreased in the DLPFC of significantly more schizophrenic subjects relative to matched controls. The reduction in DARPP-32 does not seem to be generalized to all brain regions, because a significant alteration in DARPP-32 was not observed in a separate study of caudate nucleus tissue from 12 schizophrenic subjects and their matched controls (K.A.A., H.C.H., and W.E.B., unpublished data, 1999). Similar reductions were not observed for synapsin I or CaMK II, indicating that the decrease in DARPP-32 was not attributable to a nonspecific reduction in neuronal phosphoproteins, although the possibility of a type II error must be considered. Synapsin I has been analyzed in other brain regions, and found to be altered in schizophrenic subjects. Synapsin Ia and Ib messenger RNA (mRNA) levels were elevated in the superior and left middle gyri of schizophrenic subjects younger than 75 years, while in the hippocampus, synapsin I protein levels were significantly lower. The levels of the β subunit of calcium/calmodulin-dependent protein kinase II mRNA were elevated in the frontal cortex of schizophrenic subjects; the interesting possibility that this represents a selective increase in the β subunit of calcium/calmodulin-dependent protein kinase II expression and not in CaMK Ia (this study) requires further study.

The reduction in DARPP-32 seen in schizophrenic subjects is unlikely to be the result of neuroleptic treatment. DARPP-32 in the DLPFC was not reduced in patients with AD who were treated with haloperidol compared with patients with AD who had not been treated with neuroleptic agents. Moreover, DARPP-32 was not decreased in the rat frontal cortex by long-term treatment with the neuroleptic agent raclopride. Studies using positron emission tomography have reported that dopamine D1 receptor binding is reduced in the prefrontal cortex of drug-naive schizophrenic patients. In addition, a decrease in dopamine D1 receptors was observed in the monkey prefrontal cortex in response to neuroleptic agents. Although DARPP-32 and dopamine D1 receptor expression are closely linked in the central nervous system, dopamine D1 receptor–mutant mice exhibit normal DARPP-32 expression on gross examination.

The observed reduction in DARPP-32 could be due to a selective loss of DARPP-32–containing neurons, or their processes. An increased density of neurons with a reduction in neuropil has been reported in Brodmann area 9 of schizophrenic patients. However, no change in DLPFC cell number was found in a separate study using the same brain specimens examined in this study. We cannot exclude a selective loss of a small subpopulation of DLPFC neurons that contain DARPP-32.
There are several limitations to this and other studies that use postmortem tissue analysis. A principal limitation is the small sample size for rigorous statistical analysis, although this represents one of the largest samples for this area of neuropsychiatry. Ideally, prospective enrollment of subjects should be used, an approach that is under way. Extreme efforts were made to control for the many biological parameters between subjects by individual matching of patients and control subjects. The limitations inherent in quantitative immunoblotting are discussed in the “Materials and Methods” section.

Further studies will be needed to determine whether the reduction in DARPP-32 is integral to the cause of schizophrenia or is a compensatory adaptation to the pathological features. Changes in DARPP-32 levels in experimental animals have been reported only following neurotoxic lesions of the striatum or transections of striatonigral fibers in rats or targeted deletion of the gene for DARPP-32 in mice. It will be of interest to compare schizophrenic patients with matched controls for protein levels of various downstream physiological effectors, known to be regulated by the DARPP-32/protein phosphatase 1 cascade, including voltage-dependent sodium channels, voltage-dependent L-, P-, and N-type calcium channels, the electrogenic ion pump of Na+,K+-adenosine triphosphatase, the NR1 class of NMDA receptors, 1-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, and γ-aminobutyric acid A receptors. Another component of the DARPP-32 signal transduction pathway, the NMDA receptor, may also be altered in patients with schizophrenia, because the NR2D subunit mRNA was increased in the DLPFC, but not in the parietotemporal cortex or the cerebellum, of postmortem schizophrenic brain specimens. However, studies of mRNA levels may not indicate actual levels of protein present and, therefore, must be interpreted cautiously. Other recent studies have reported alterations in NMDA, 1-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, and kainate receptor mRNA levels in various cortical regions in schizophrenic subjects. (Meador-Woodruff and Healy provide a review.) However, these findings have been inconsistent.

In summary, our major finding suggests a selective decrease of DARPP-32 protein levels in the DLPFC of schizophrenic patients. DARPP-32 is a key regulatory phosphoprotein involved in the control of receptors, ion channels, and transcription factors; it is reciprocally activated and deactivated by reversible phosphorylation regulated by the 2 neurotransmitter systems most consistently implicated in the pathophysiological features of schizophrenia (Figure 1). The DLPFC has alterations in white matter interstitial neuron number and abnormalities in the glutamate and γ-aminobutyric acid systems in schizophrenia. The observed abnormality in DARPP-32 in the DLPFC could contribute to the compromised function of the cognitive-affective parallel DLPFC circuit in patients with schizophrenia. Thus, decreased availability in the compromised DLPFC circuit of the DARPP-32 protein required for the regulation of critical downstream receptor and ion channel functions could contribute to the profound frontal cognitive deficits observed in patients with schizophrenia.

Figure 4. Ratios of phosphoprotein levels in the dorsolateral prefrontal cortex from patients with Alzheimer disease. The average ratios for each protein were determined by immunoblotting, as described in the “Materials and Methods” section (n=4). Each ratio represents the protein level from a patient treated with the antipsychotic haloperidol divided by the protein level from a matched patient not treated with any antipsychotic medication. A, DARPP-32; B, The α subunit of calcium/calmodulin-dependent protein kinase II; C, Synapsin I.

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