



Prominent increased calcineurin immunoreactivity in the superior temporal gyrus in schizophrenia: A postmortem study



Akira Wada^{a,b,*}, Yasuto Kunii^{a,c}, Jyunya Matsumoto^a, Mizuki Hino^a, Qiaohui Yang^a,
Shin-ichi Niwa^{a,c}, Hirooki Yabe^a

^a Department of Neuropsychiatry, Fukushima Medical University School of Medicine, 1 Hikarigaoka, Fukushima City, Fukushima 960-1295, Japan

^b Department of Neuropsychiatry, The University of Tokyo Hospital, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

^c Departments of Psychiatry, Aizu Medical Center, Fukushima Medical University, 21-2 Maeda, Tanisawa Kawahigashimachi, Aizuwakamatsu city, Fukushima 969-3492, Japan

A B S T R A C T

Many neuroimaging studies have demonstrated structural changes in the superior temporal gyrus (STG) in patients with schizophrenia. Several postmortem studies have reported on the pathogenesis of schizophrenia, but few reports have investigated alterations in molecules in the STG. In addition, several studies have suggested that calcineurin (CaN) inadequacy may be a risk factor for schizophrenia, but no reports about CaN expression in the STG in schizophrenia have been published. We compared the density of CaN-immunoreactive (CaN-IR) neurons in the STG from 11 patients with schizophrenia with that of 11 sex- and age-matched controls. We used immunohistochemical analysis with rabbit polyclonal antibodies against human CaN. In the STG, the density of CaN-IR neurons in layers II–VI in the group with schizophrenia was significantly higher than that in the control group. Our results confirmed pathological changes in the STG in patients with schizophrenia, suggesting that alterations in the CaN pathway play a role in the pathogenesis of schizophrenia.

1. Introduction

Although the etiology of schizophrenia remains unclear, two leading hypotheses exist. One is the dopamine hypothesis (Carlsson, 1978), and the other hypothesis involves *N*-methyl-D-aspartate (NMDA) receptor hypofunction (Javitt and Zukin, 1991). Dopamine signaling is regulated by dopamine- and cAMP-regulated phosphoprotein 32 (DARPP-32) (Greengard et al., 1999). Calcineurin (CaN) has phosphatase activity, it de-phosphorylates DARPP-32 (Addy et al., 2007). CaN inhibits signal transmission from dopamine receptors by phosphorylating DARPP-32. Because CaN is activated by Ca⁺⁺ inflow through NMDA receptors, NMDA receptor hypofunction leads to hypofunction of CaN by indirect mechanism (Greengard et al., 1999). CaN signaling is closely related to dopamine-NMDA receptor signal transduction. CaN is comprised of a catalytic (CaN A) and a regulatory (CaN B) subunit, which are both important in intracellular signal transmission (Rusnak and Mertz, 2000). This protein is present widely in the nervous system accounting for more than 1% of the total protein content of brain tissue (Guerini, 1997). CaN A is mainly localized in the cerebral cortex, striatum, hippocampus, and cerebellum. However, there is no CaN A in thalamic and hypothalamic neurons (Solà et al.,

1999).

Recently, several reports have implicated CaN malfunction as a possible risk factor for schizophrenia. Gerber et al. reported a genetic association between schizophrenia and a genetic variation of *PPP3CC*, the gene encoding the CaN catalytic subunit (Gerber et al., 2003). The other study using transgenic mice reported multiple abnormal activities associated with schizophrenia such as increased locomotor activity, decreased social interaction, and impairments in prepulse inhibition and latent inhibition (Zeng et al., 2001; Miyakawa et al., 2003). Nevertheless, only a few reports examining the expression of CaN protein in the central nervous system of patients with schizophrenia have been published. We previously examined the histological and cellular expression of CaN in the dorsolateral prefrontal cortex (DLPFC), hippocampus, caudate, and putamen using postmortem schizophrenia brains. We found an increased ratio of CaN-immunoreactive (IR) neurons in the caudate nucleus of patients with schizophrenia (Wada et al., 2012). In addition, we previously examined postmortem brains of patients with schizophrenia and investigated expression of DARPP-32, a key molecule in dopaminergic and glutamatergic neuronal transduction that is closely associated with CaN. The density of DARPP-32-IR neurons was significantly lower in layers II–V

* Corresponding author at: Department of Neuropsychiatry, Fukushima Medical University School of Medicine, 1 Hikarigaoka, Fukushima City, Fukushima 960–1295, Japan.
E-mail address: nishityo4nishihara@gmail.com (A. Wada).

Table 1

Demographic information of schizophrenic patients and matched controls.

Subject	Sex	Age	PMI(h)	Preservation(y)	DOI(y)	Brain weight(g)	Cause of death	Estimated total dosage of neuroleptics and anticholinergics prescribed (mg)	
Schizophrenia									
1	M	39	33.0	1	25	1260	Suicide	1414375	912500
2	F	39	20.0	2	23	1370	Gastric sarcoma	5078075	524870
3	M	48	8.0	2	33	1396	Pneumonia	25053600	903375
4	M	58	6.0	1	30	1320	Gastric cancer	15625650	3832500
5	M	66	7.0	3	36	1378	Pneumonia	0	0
6	M	70	28.0	6	39	1334	Pancreatic cancer	7829250	1950195
7	M	70	19.0	4	39	1348	Pneumonia	7587255	2135250
8	M	71	13.0	1	48	1185	Pneumonia	5308560	262800
9	M	73	17.5	2	52	1114	Pneumonia	2277600	0
10	M	75	17.0	5	47	1157	Pneumonia	3859875	3859875
11	F	87	3.5	5	49	1184	Suffocation	0	0
Total	9M/2F	67 ± 14	14.8 ± 7.7	3 ± 2					
Control									
1	F	40	13.0	2		1260	Acute heart failure		
2	M	44	9.0	2		1546	Acute heart failure		
3	M	46	25.0	1		1450	Sudden death		
4	M	50	21.0	4		1395	Acute heart failure		
5	M	53	7.0	2		1398	Lung cancer		
6	M	62	12.0	5		1570	Tongue cancer		
7	M	71	2.0	3		1600	Malignant mesothelioma		
8	M	71	2.0	5		1373	Pneumonia		
9	M	72	13.0	4		1300	Lung cancer		
10	M	72	5.5	4		1329	Lung cancer		
11	F	80	5.0	1		1140	Septic shock		
Total	9M/2F	60 ± 13.9	13 ± 6.9	3 ± 1.5					

PMI=postmortem interval, DOI=duration of illness (years).

Estimated total lifetime drug consumption=DOI×365×dose of drugs (during 3 months before death). Neuroleptic doses are represented as chlorpromazine equivalents (mg). Anticholinergic doses are represented as promethazine equivalents (mg).

of the DLPFC in patients with schizophrenia (Kunii et al., 2011a). In addition, expression of both DARPP-32 and Thr34-phosphorylated DARPP-32 was decreased in the superior temporal gyrus (STG) of postmortem schizophrenia brains (Kunii et al., 2011b).

Although molecular and imaging studies have reported abnormalities in schizophrenia in the STG, few studies have described these abnormalities using postmortem brains. The Heschl gyrus (HG) located in the STG plays an important role in auditory perception (Zattore and Binder, 2000). Dierks et al. demonstrated that HG activation was related to auditory hallucinations in patients with schizophrenia using functional MRI (Dierks et al., 1999). The STG is the principal generator of mismatch negativity (MMN), which occurs through the comparison process between sound deviation and the neural trace of preceding sounds stored in auditory sensory memory that is located in the STG (Näätänen et al., 2007). NMDA receptor transmission is assumed to generate MMN because NMDA antagonists attenuate the magnitude of MMN (Javitt et al., 1996). Actually, some studies have reported dysfunction of glutamate systems in the STG. Le Corre et al. reported increased mRNA expression of the NMDA receptor NR1 subunit splice variant in postmortem schizophrenic brains in the STG (Le Corre et al., 2000). In addition, increased NMDA receptor density was reported using ligand binding studies (Nudmamud and Reynolds, 2001).

Taken together, the STG was involved in auditory hallucinations in patients with schizophrenia. Our previous study reported that DARPP-32 was decreased in the STG. We have previously reported that elevations to CaN in the caudate may be caused by buffering actions against excessive dopamine transduction (Wada et al., 2012). We hypothesized that CaN immunoreactivity might be elevated in the STG in patients with schizophrenia as a secondary change following decreasing DARPP-32 immunoreactivity.

We investigated postmortem brains from patients with schizophrenia with specific CaN Antibodies to clarify the expression of CaN in the

STG. Because each cortical layer shows different neural connections and functions, precise immunohistochemical analysis is crucial to determining histological and cellular localizations of target molecules. Immunohistochemical analyses in each layer could only be performed using postmortem tissues.

2. Methods

2.1. Brain tissue

Postmortem brain sections from patients with schizophrenia were obtained from the Fukushima Brain Bank at the Department of Neuropsychiatry, Fukushima Medical University. Normal postmortem brain tissues were obtained from autopsy cases in the Section of Pathology, Fukushima Medical University Hospital. These samples were the same samples used by Kunii et al. in a previous report (Kunii et al., 2011b). This study was approved by the Ethics Committee of Fukushima Medical University and complied with the Declaration of Helsinki. All procedures were carried out with adequate understanding and written consent of the next of kin (e.g. parents, children, spouse). The samples used in this study were obtained from 11 patients with schizophrenia and 11 controls (Table 1). No differences were observed in average age, sex ratio, or postmortem interval (PMI) between the two groups. All patients with schizophrenia satisfied the diagnostic criteria established by the American Psychiatric Association (Diagnostic and Statistical Manual of Mental Disorders: DSM-IV). All schizophrenia patients had no history of neurological disorders or substance abuse, except for a smoking habit. In addition, none of the control subjects had any episodes of psychiatric disorders, neurological disorders, or substance abuse, except for a smoking habit. All brains were investigated carefully by neuropathologists and revealed no indication of neurological disorders in this study, although mild senile changes such as unremarkable senile changes comprising ubiquitin-

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