

Lectin-Positive Spherical Deposits (SPD) Detected in the Molecular Layer of Hippocampal Dentate Gyrus of Dementia, Down's Syndrome, and Schizophrenia

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Abstract

Lectins are proteins which specifically bind (or crosslink) carbohydrates. Recent studies have shown the importance of glycosylation in pathogenesis of diseases. Lectin-positive spherical deposits (SPD), 3-10 micron in diameter, have been detected in the molecular layer of dentate gyrus of hippocampus in dementia, Down's syndrome, and schizophrenia. In schizophrenia, SPD was observed without exception, regardless of having history of pharmacotherapy. Multi-labeling histochemical methods, revealed that single strand DNA was co-localized in hippocampal SPD of schizophrenia with lectin, including GSI-B4 for galactose, and UEA-I for fucose, suggesting that SPD formation in schizophrenia is related to apoptotic process. The molecular basis of SPD formation should be investigated in brains with neuropsychiatric illnesses, including Alzheimer's disease and Parkinson's disease.

Keywords: Sugar chain; Post-mortem brain; Apoptosis; Dentate gyrus; Hippocampus; Schizophrenia

Introduction

Hippocampal neuropathology, as a result of pathognomonic procedures of molecular basis related to memory and cognitive disturbance, has been described in mental disorders such as schizophrenia [1]. Glycoconjugates have been implicated to play a major role in the process of cell-cell recognition of development during embryogenesis. Recently, increasing number of diseases come to be known to be caused by abnormalities in the biosynthesis of sugar chains [2]. Abnormal accumulation or deposition of the sugar chains in brains of patients with neurodegenerative diseases has been reported [3].

Lectin staining is able to reveal several kinds of carbohydrate-related depositions in addition to the conventional degenerative changes including senile plaques, neurofibrillary tangles and corpora amylacea (Table 1, Figure 1) [4]. According to an old definition, "Lectins are multivalent carbohydrate-binding proteins or glycoproteins except for enzymes and antibodies." As a significant number of exceptions are evident now, such a narrow definition, however, seems no longer relevant. For today, "lectins are defined as proteins which specifically bind (or crosslink) carbohydrates." The authors detected lectin-positive

spherical deposits (SPD) in the molecular layer of hippocampal dentate gyrus of schizophrenia (Figures 1-3), dementia, and Down's syndrome (Figure 4) [4]. In the present mini-review, possible nature and pathophysiological significance of lectin-positive SPD would be introduced.

Spherical Deposits (SPD) in the Molecular Layer of Hippocampal Dentate Gyrus

Lectin immunohistochemistry using various antibodies that detects carbohydrates (Table 1), combined with conventional staining methods, revealed SPD, 3-10 micron in diameter, in the molecular layer of the dentate gyrus of the hippocampal formation (Figures 1-3) from patients with Alzheimer's disease (dementia of Alzheimer type), dementia with tangles, Down's syndrome and schizophrenia, and aged individuals (Figure 4) [2].

The lectin-positive SPD did not show immunoreactivity for antibodies against ubiquitin and tau-protein, though the corpora amylacea showed clear immunoreactivity for these substances (Figure 1D-b) [4]. The SPD contained fucose (α -Fuc), galactose (α -Gal) (Figures 2C, 6), N-acetyl galactosamine (α -GalNAc) (Figure 5), N-acetyl glucosamine (GlcNAc), sialic acid, mannose (Man) and chondroitin sulfate (Figure 1D-a), suggesting that there might be unusual glycometabolism (Table 1), possibly related to the process

Lectin and antibodies	Abbreviation	Carbohydrate binding specificity
Archis hypogaea agglutinin	PNA	Gal(β 1,3)GalNAc
Canavalia ensiformis agglutinin	Con A	Branched α -Man (Man α 1-6 (Man α 1-3) Man)
Datura stramonium	DSA	GlcNAc
Dolichos biflorus agglutinin	DBA	α -GalNAc
Erythrina cristagalli	ECA	Gal(β 1,3)GlcNAc
Glycine max agglutinin	SBA	GalNAc(α 1,3)Gal
Griffonia simplicifolia iso agglutinin I-B4	GSI-B4	α -Gal
Pisum sativum agglutinin	PSA	Fuc(α 1,6)Glc, α -Man
Triticum vulgare	WGA	Man β (1,4)GlcNAc(1,4)GlcNAc
Ulex europaeus agglutinin	UEA-I	α -Fuc

Table 1: Interaction between lectins and antibodies, abbreviation, and the carbohydrate binding specificity is shown.

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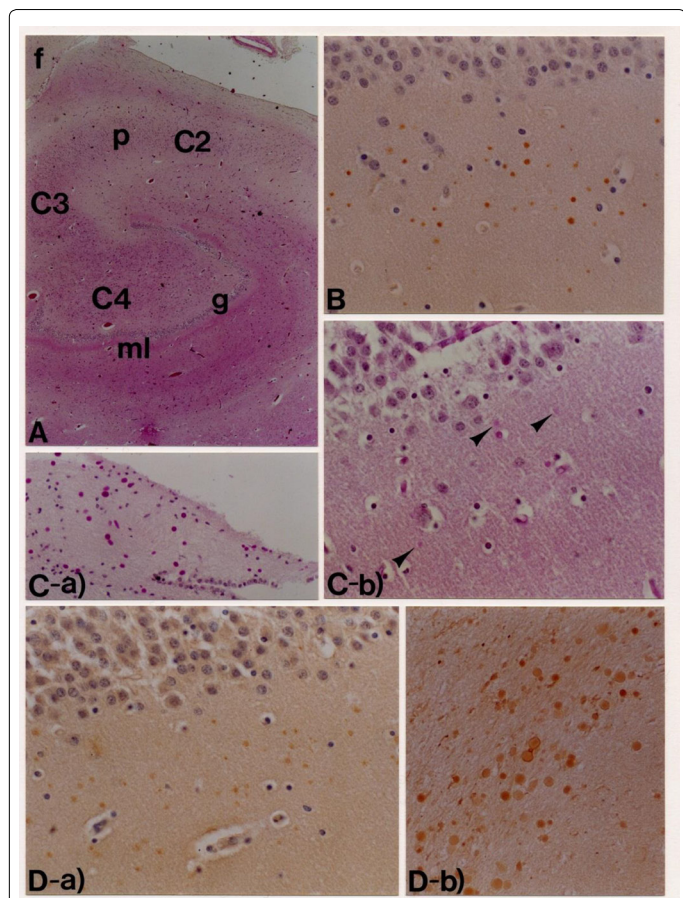


Figure 1:
 A: The hippocampal formation stained by Hematoxylin Eosin.
 g: granular layer
 p: pyramidal neuron ml: molecular layer
 f: fimbria
 B: SPD detected by lectin stains. GSI-B4.
 C-a: Corpora amylacea are intensely stained by PAS.
 C-b: SPD are weakly stained by PAS.
 D-a: SPD show intense reactivity with anti-chondroitin sulfate.
 D-b: Corpora amylacea show intense reactivity with anti-tau protein antibody.

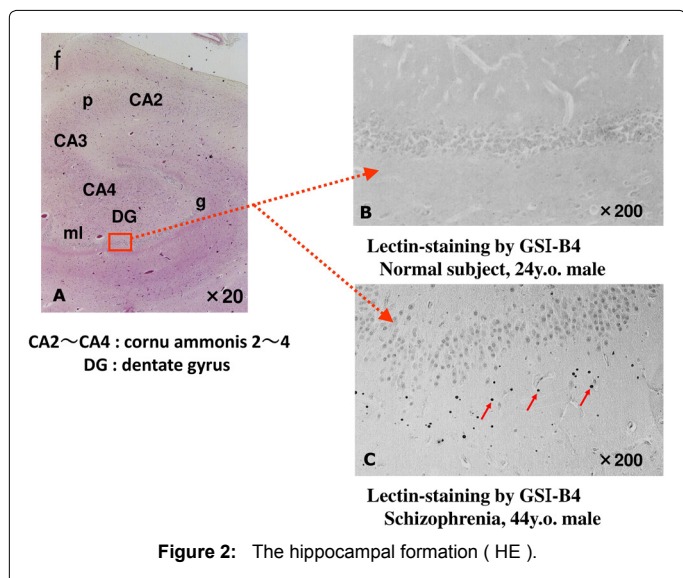


Figure 2: The hippocampal formation (HE).

of neurogenesis in the molecular layer of hippocampal dentate gyrus (Figures 5-7).

Lectin-Positive SPD in Schizophrenia

In the brains of patients with schizophrenia, the lectin-positive SPD was observed in the molecular layer of the dentate gyrus of the

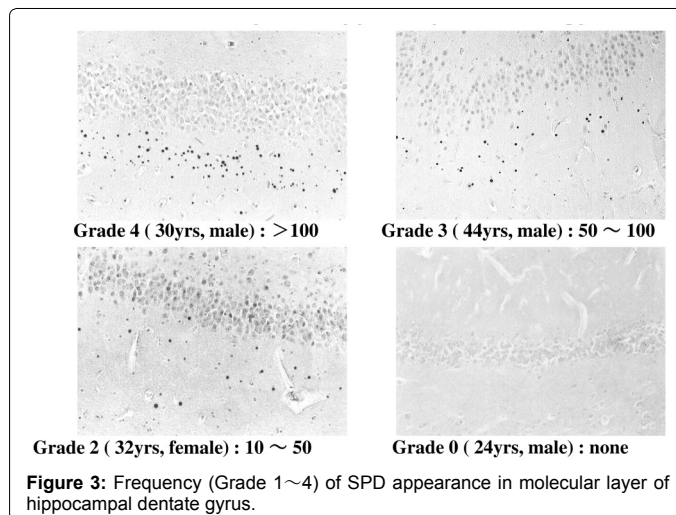


Figure 3: Frequency (Grade 1~4) of SPD appearance in molecular layer of hippocampal dentate gyrus.

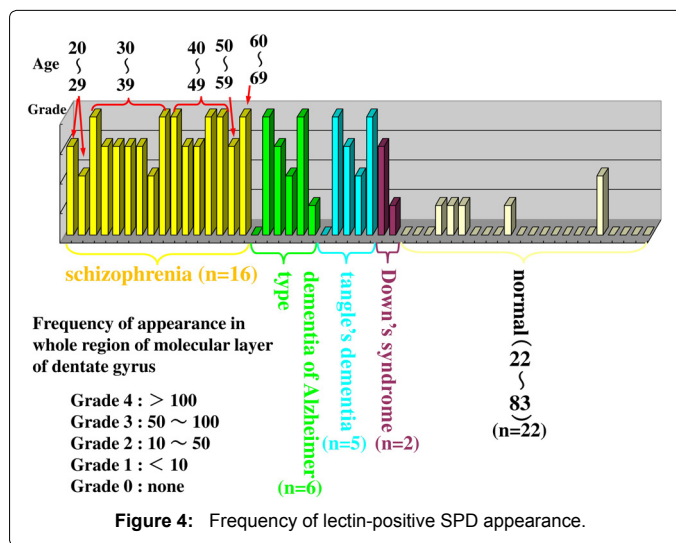


Figure 4: Frequency of lectin-positive SPD appearance.

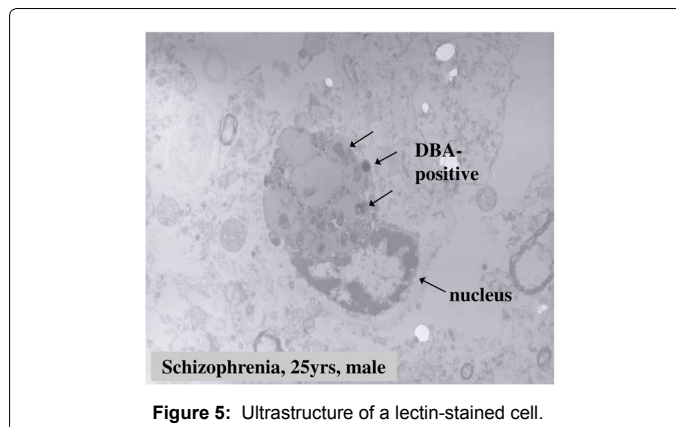
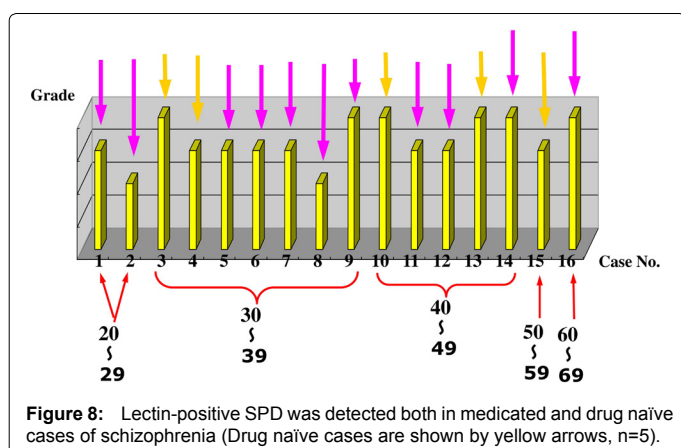
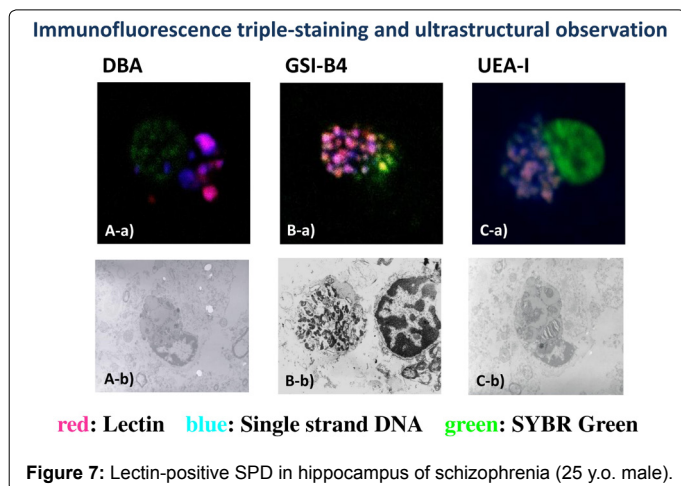
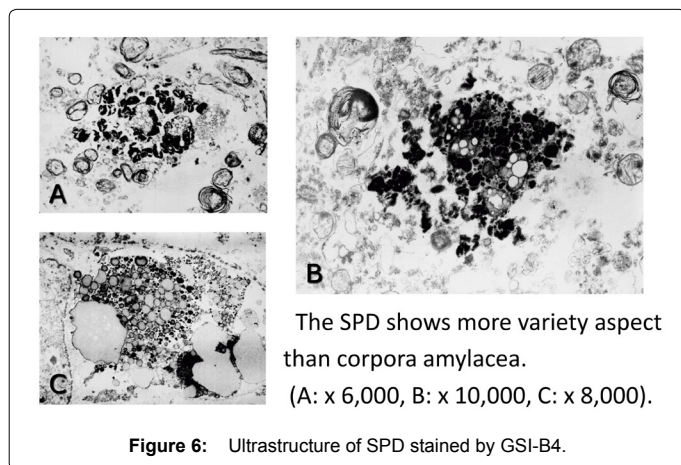


Figure 5: Ultrastructure of a lectin-stained cell.



hippocampal formation, without exception, regardless of previous medication of antipsychotics (Figure 8). In the lectin-positive SPD, partially disrupted nucleus with decreased staining properties by mean of SYBR Green, a marker of DNA, were detected. Single strand DNA and lectin, including BSI-B4 for galactose (Figures 7B-a, 7B-b), UEA-I for fructose (Figure 7C-a, 7C-b), and DBA for N-acetyl galactosamine (Figures 7A-a, 7A-b) were co-stained in the portion of partially disrupted nucleus (Figures 7, Table 1). In immuno-electron microscope method, lectin-positive structures were also detected in the portion of partially disrupted nucleus (Figure 5,6, 7A-b, 7B-

7C-b). These lectin-positive SPD might be produced in the process of apoptosis (Figures 7) [3,5]. Some experimental studies reported that a kind of therapeutic products of major tranquilizers induced neuron apoptosis [6]. However, it is unclear whether hippocampal lectin-positive SPD in non-schizophrenia cases has similar molecular basis to that in schizophrenia.

Lectin-Positive SPD in Dementia

In Alzheimer's disease, and tangle's dementia, some cases did not contain hippocampal lectin-positive SPD, being different from schizophrenia (Figure 4). The chemical nature or formation procedures of lectin-positive SPD in dementia, as degenerative disorders, and the distinction between that in natural aging processes also remains to be investigated.

Discussion

Recent studies have shown more and more importance of the involvement of altered glycosylation in pathological procedures of neuropsychiatric diseases. In the superior temporal gyrus, altered N-glycosylation of GABAA receptor has been shown in schizophrenia [7]. In our study, it should be noticed that lectin-positive SPD in the molecular layer of dentate gyrus of hippocampal formation in patients with schizophrenia is observed also in drug naïve cases, though some experimental studies showed that a kind of therapeutic products of major tranquilizers induced neuron apoptosis in the dentate gyrus. The molecular basis of lectin-positive SPD formation of schizophrenia, possibly linked with apoptotic process, and may also related to neurodevelopment should further be elucidated. The nature of lectin-positive SPD of non-schizophrenia cases, such as Parkinson's disease, dementia, Down's syndrome, etc. (Figure 4) should also be examined.

As novel therapeutic strategies, some pharmacodynamic studies have recently shown the usefulness of exogenous lectin for brain delivery of intranasally administered drugs of neuropsychiatric diseases such as schizophrenia [8] and Parkinson's disease [9]. This leads us to further examine lectin pathology as well as lectin physiology to establish novel methods for diagnoses and treatment of neuropsychiatric illnesses.

Conclusion

To clarify the pathophysiology of degenerative disorders including Parkinson's disease as well as Alzheimer's disease, and to detect newly established biomarkers of neurodegeneration, the nature of lectin-positive SPD should further be analyzed.

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