め，病院であれば研究が可能である。また，マーカーが開発された際には，発展途上国でも対応できる可能性がある。

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Analyses of Fyn-tyrosine kinase and NMDA-R in the post-mortem brains of schizophrenia

Hattori K, Tanaka H, Wakabayashi C, Uchiyama H, Yamamoto N, Hori H, Teraishi T, Sasayama D, Kunugi H

Dept Mental Disorder Research, National Inst Neurosci, Nat Center Neurol & Psychiatry, Japan

Summary

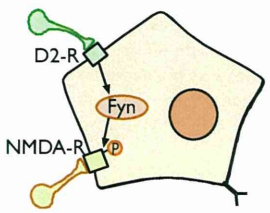
•Fyn's function: Learning, LTP, dopamine signaling
•Fyn's substrate: GRIN2B (NMDA-R subunit)
→Evaluation of Fyn, NMDA-R in Schizo brain

Main findings	Schizo brain
Fyn, Fyn activity	Increased
GRIN1	Unchanged
GRIN2A & 2B	Decreased

•GRIN2A & 2B reduction: Might reflect NMDA-R hypofunction, decreased synapses in Schizophrenia

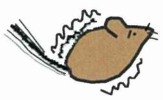
Introduction

Fyn kinase is a key mediator of the crosstalk between D2-R and NMDA-R



Hattori et al., JBC, 2006

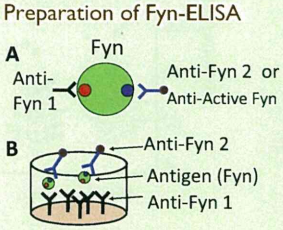
Features of Fyn-deficient mice



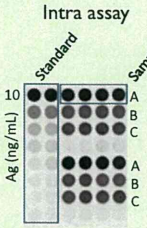
- Deficits in LTP, cognition
- Defective maternal behavior
- Fearful
- Lower sensitivity to ethanol
- Lower sensitivity to haloperidol

Method

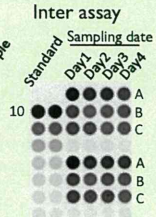
Preparation of Fyn-ELISA



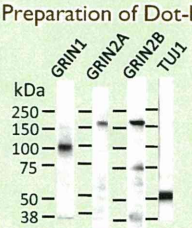
Intra assay



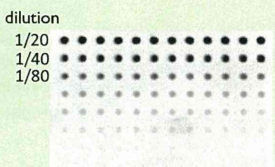
Inter assay



Preparation of Dot-blot



Bio-dot (Bio Rad)



Sample

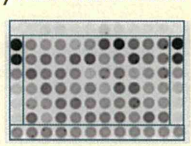
Stanley Neuropathology Consortium (BA6)

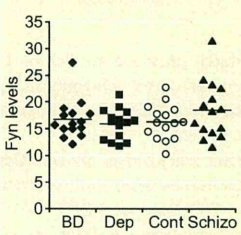
Sampl	Nos
Bipolar	15
Dep	15
Control	15
Schizo	15

Blind analyses
↓
Uncode after data submission

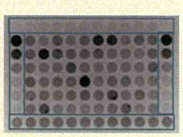
Results

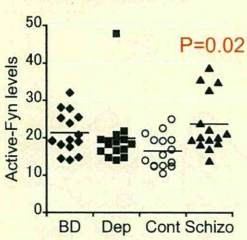
Fyn sandwich ELISA





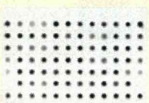
Active-form Fyn



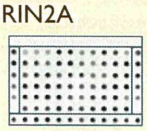


ANCOVA(storage time, post mortem interval)

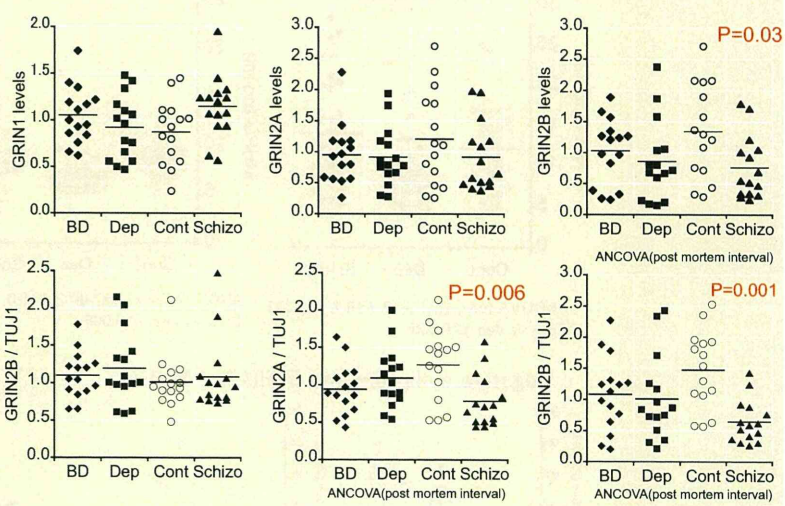
GRIN1



GRIN2A



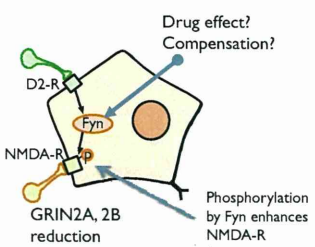
GRIN2B



Other results

•No difference among diagnostic groups in the mRNA levels of fyn, GRIN1, GRIN2A or GRIN2B.
•Risperidone treatment did not affect GRIN1, GRIN2A or GRIN2B protein levels in the frontal cortices of mice.

Discussion



•The GRIN2A/2B reduction might be the cause of NMDA-R hypofunction, which has been hypothesized in schizophrenia pathophysiology.

•Increased Fyn might be a result of antipsychotic treatment or a compensatory consequence of reduced NMDA-R function.

•Analyses using larger sample size are now underway.

Acknowledgements

Postmortem brain tissue was donated by The Stanley Medical Research Institute

Analyses of monoamine metabolites in the cerebrospinal fluid of patients with schizophrenia and depression

Hattori K, Sasayama D, Teraishi T, Fujii T, Tanaka H, Kunugi H

Department of Mental Disorder Research, National Institute of Neuroscience, National Center Hospital of Neurology and Psychiatry, Japan

Summary

•We evaluated the levels of monoamine metabolites in the CSF of patients with schizophrenia and depression.

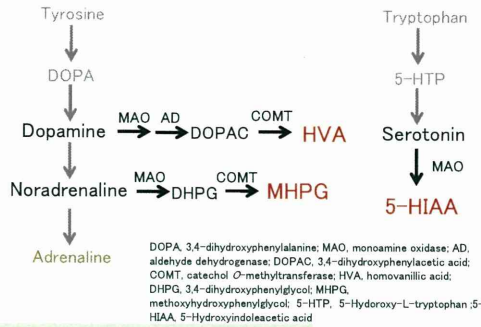
	HVA	MHPG	5-HIAA
Schizophrenia	↑	→	→
Depression	→	↓	↓

These changes supposed to be the effect of medication

•Among the schizophrenic patients,
higher HVA → lower positive symptoms
higher 5-HIAA/MHPG → higher negative symptoms
severer side effects (EPS)

•CSF monoamine levels could be used as biomarkers for response to antipsychotic medication.

Introduction



DOPA, 3,4-dihydroxyphenylalanine; MAO, monoamine oxidase; AD, aldehyde dehydrogenase; DOPAC, 3,4-dihydroxyphenylacetic acid; COMT, catechol *O*-methyltransferase; HVA, homovanillic acid; DHPG, 3,4-dihydroxyphenylglycol; MHPG, methoxyhydroxyphenylglycol; 5-HTP, 5-Hydoroxy-L-tryptophan ;5-HIAA, 5-Hydroxyindoleacetic acid

•Monoamine neurotransmitters play crucial roles in psychiatric disorders. The levels of monoamine metabolites, i.e., HVA, MHPG and 5-HIAA in the cerebrospinal fluid (CSF), reflect the release of dopamine, noradrenalin and serotonin respectively in the brain.

•This study was aimed to examine the possible use of CSF monoamine metabolites as biomarkers for schizophrenia and depression.

Method

Subjects

•Patients: Consensus diagnosis by 2 psychiatrists (DSM-IV)

•Controls: Recruited through advertisements in free local magazines and our website.

•Past history were ruled out by Mini-International Neuropsychiatric Interview.

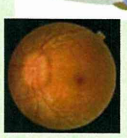
	No.
Schizophrenia	35
Depression	35
Control	32
Total	102

All patients were medicated.

Neurological assessments

•Jolt accentuation

•Ophthalmoscopy: Papillary edema, Pulse of central retinal vein



Lumbar puncture

•Lateral position, L4/5

•With local anesthesia

Psychiatric assessments

•Schizophrenia: PANSS

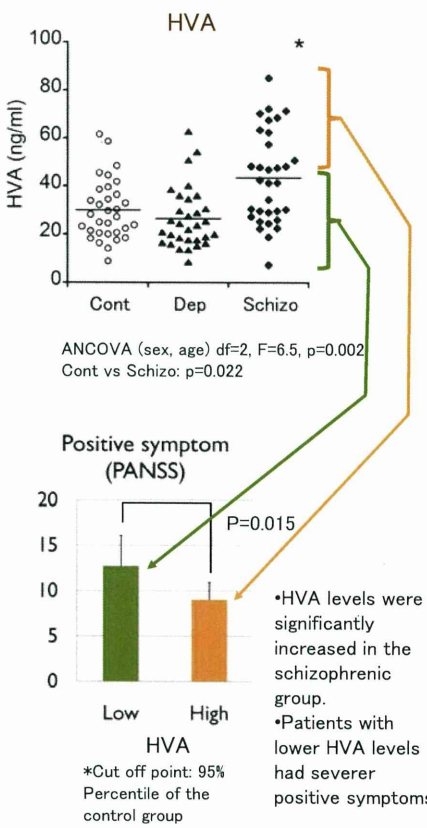
•Depression: HDRS

•Side effect: DIEPSS

Analyses of CSF HVA, MHPG and 5-HIAA levels.

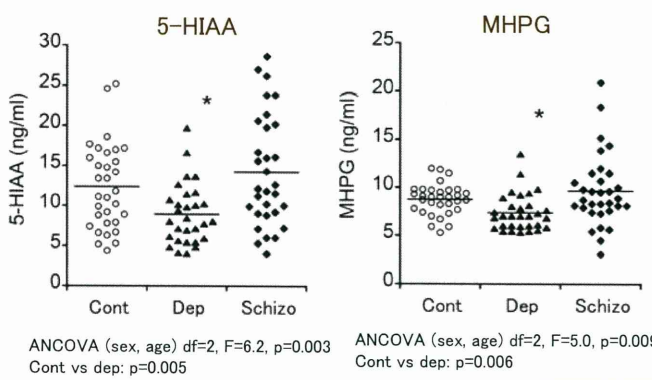
The levels of monoamine metabolites were analyzed by high performance liquid chromatography (HPLC) by SRL Inc. (Medical laboratory testing company)

Results



•HVA levels were significantly increased in the schizophrenic group.

•Patients with lower HVA levels had severer positive symptoms

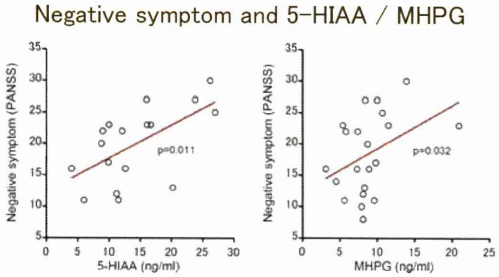


•5-HIAA / MHPG levels did not differ between schizophrenia and the controls.

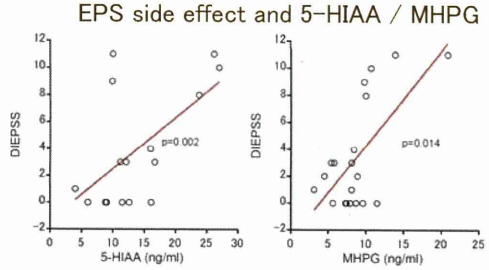
•5-HIAA / MHPG levels were significantly decreased in depression.

•Among schizophrenic group, 5-HIAA / MHPG levels correlated with negative symptoms or severer extra pyramidal symptoms.

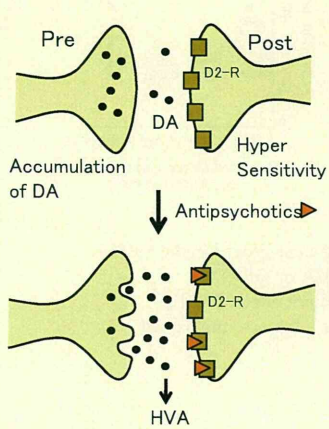
Negative symptom and 5-HIAA / MHPG



EPS side effect and 5-HIAA / MHPG



Discussion



•Most previous studies on CSF HVA levels in unmedicated schizophrenic patients reported no significant difference between patients and controls.

•Several studies showed that the HVA levels increased after antipsychotic medication.
→The enhanced CSF HVA levels in our schizophrenic patients supposed to be the effect of antipsychotic medication. (Left figure).

•Similarly, most previous studies on CSF 5-HIAA levels in unmedicated depression reported no significant difference between patients and controls, and the 5-HIAA levels increased after antidepressant medication. Therefore, reduced 5-HIAA levels in the depression could be due to medication.

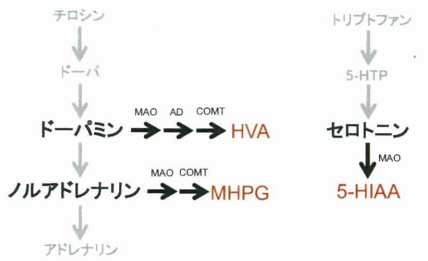
•Correlations of monoamine levels with symptoms and adverse effects in the schizophrenia patients suggest that the CSF monoamine levels could be used as biomarkers for response to antipsychotic medication.

気分障害CSF中アミン代謝産物の解析

国立精神・神経医療研究センター
神経研究所　疾病研究第３部

○服部功太郎, 篠山大明, 寺石俊也, 吉田寿美子, 功刀浩

アミン系伝達物質の代謝経路



対象

- 統合失調症
- 気分障害

} 院内ポスター
主治医からの紹介

- 健常対照 ⟶ フリーペーパー
インターネット

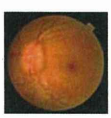
精神科的診察

- M.I.N.Iにて診断
- 症状評価： PANSS, HAM-D
- 副作用: DIEPSS

腰椎穿刺

安全性の確保

- 髄膜兆候等の除外
- 眼底検査(拍動確認)



苦痛の軽減

- 十分な麻酔
→痛みは採血と同等

有害事象への対応

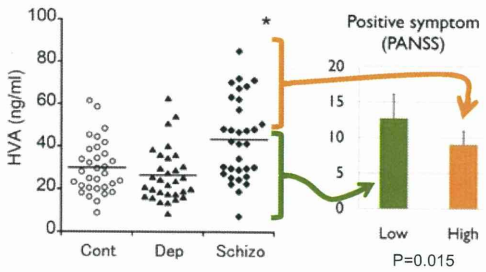
- 24時間電話対応
- 医療補償

検体収集状況

	検体数	症例数
統合失調症	56	38
気分障害	47	42
健常対照	44	40
その他	3	3
Total	150	121

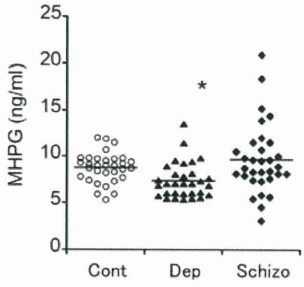
結果

HVA（ドーパミン産物）



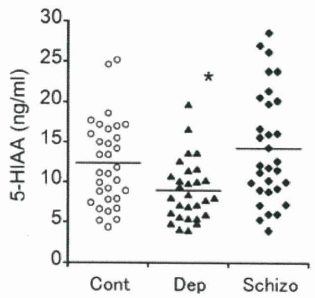
ANCOVA (sex, age) df=2, F=6.5, p=0.002
Cont vs Schizo: p=0.022

MHPG（ノルアドレナリン産物）



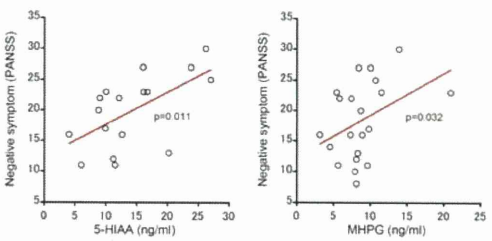
ANCOVA (sex, age) df=2, F=5.0, p=0.009
Cont vs dep: p=0.006

5-HIAA（セロトニン産物）

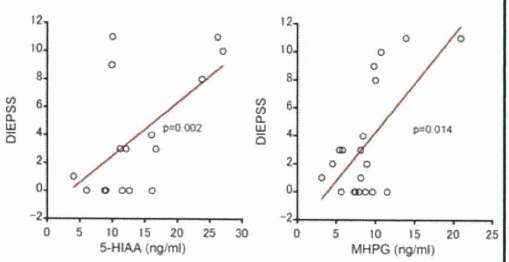


ANCOVA (sex, age) df=2, F=6.2, p=0.003
Cont vs dep: p=0.005

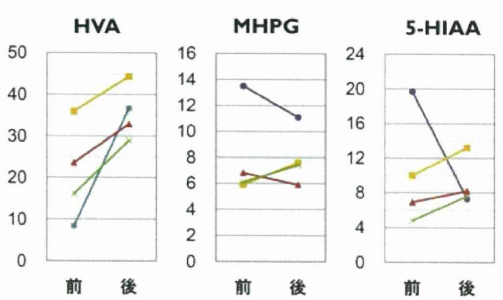
Sz 陰性症状と5-HIAA, MHPG



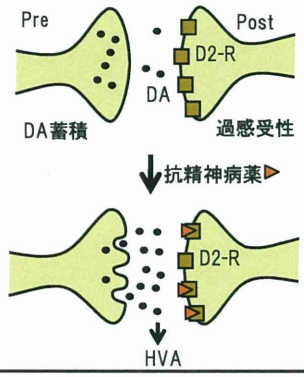
Sz EPS副作用と5-HIAA, MHPG



ECT前後のアミン代謝産物



統合失調症におけるHVA↑



うつにおける5-HIAA↓