

# 学位論文の要旨

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学位論文名 Evaluation of Autonomic Nervous System by Salivary  
Alpha-Amylase Level and Heart Rate Variability in Patients With  
Schizophrenia

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## 論文内容の要旨

### **INTRODUCTION**

During the onset and progression of schizophrenia, there are many signs of dysfunction of the autonomic nervous system (ANS). That suggests the possibility of an imbalance between sympathetic and parasympathetic activity. As the relative stability of internal environment depends largely on the functioning of the ANS, even a slight disorder of the ANS could induce a wide range of neuropsychophysiological disorders. Therefore, a practical method to evaluate sympatho-vagal activity would be useful in clinical sciences. Several studies have also shown alterations in ANS using electrophysiological methods such as electrodermal measures and heart rate variability (HRV). These studies have demonstrated decreasing of the ANS in patients with schizophrenia.

On the other hand, salivary alpha-amylase (sAA) has recently been considered to be a useful marker for evaluating the sympathetic-adrenal-medullary (SAM) system. Several studies reported a significant increase in sAA following psychosocial stress, indicating the association of high stress levels with higher sAA. When sudden stressful stimuli occur, sympathetic fibers trigger the salivary glands, which secrete amylase within minutes. Therefore, sAA has the potential to be useful as a marker of autonomic activity because salivary gland secretion is regulated by both SNS and PNS. There was a study that reported that the sAA level

was increased significantly in patients with schizophrenia compared to controls and that the correlation between the sAA level and psychotic state was highly significant in patients with schizophrenia. However, there is little evidence as to which branch (sympathetic or parasympathetic) of the ANS is predominant in the increases in sAA. We investigated ANS function represented in patients with schizophrenia by measuring sAA and HRV.

## **MATERIALS AND METHODS**

The study subjects consisted of 25 patients with schizophrenia and 25 healthy controls, who were recruited from October 2010 to March 2011. Schizophrenia symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS). First, subjects were measured sAA activity by using hand-held monitor. Next, HRV was checked with a hand-held device consecutively. Five min electrocardiogram segments were obtained, and power spectra were automatically created via a fast Fourier transformation. The resulting spectrum was integrated, and areas associated with discrete frequency bands were obtained from the output of the device: low frequency (LF: 0.04-0.15 Hz) of HRV representing both SNS and PNS activity; high frequency (HF: 0.15-0.4 Hz) of HRV associated almost entirely with PNS activity; total power (TP: 0.03-0.4 Hz) representing overall ANS activity.

## **RESULTS AND DISCUSSION**

The sAA activity in the patients was significantly higher than that in the controls ( $p < 0.001$ ). Furthermore, the correlation between sAA level and psychiatric symptoms was highly significant ( $P = 0.02$ ).

With respect to differences in the HRV between the two groups, spectral powers, which mainly reflect PNS activity, were markedly lower in the schizophrenia group than in the control group (HF,  $p = 0.007$ ). However, there were no significant differences between two groups in the spectral powers that reflected mainly SNS activity (LF/HF,  $p = 0.47$ ).

In the present study, we found that the sAA levels in patients with schizophrenia were significantly higher than those of normal healthy controls and that the sAA level increased significantly with increases in psychotic state. With respect to differences in the HRV between the two groups, spectral powers, which mainly reflect PNS activity, were markedly lower in the schizophrenia group than in the control group. However, there were no significant differences between two groups in the spectral powers that reflected mainly SNS activity. We suggest that the sAA level is increased mainly by inhibition of PNS activity and that SNS shows relatively high activity. We also consider that measurement of the sAA level may be a useful marker for assessment of the severity of schizophrenia. Further research with additional subjects is clearly necessary because the mechanism of schizophrenia, especially dysfunction of the

sympatho-parasympathetic balance, is still poorly understood.

### **CONCLUSION**

The results of this study indicate that the reduced PNS function is characterized by increase in sAA level in patients with schizophrenia. These findings imply that PNS activity might be suppressed and the SNS shows relatively high activity in patients with schizophrenia.

論文審査及び最終試験又は学力の確認の結果の要旨

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論文審査の結果の要旨

統合失調症は難治性疾患であり、その病態や原因については、神経伝達物質機能異常、神経発達障害、神経炎症仮説、遺伝性発症脆弱性、ストレス脆弱性などが挙げられるが、これまでに一致した見解は得られていない。また、統合失調症の発症や臨床経過において、自律神経系の異常が指摘されており、唾液アミラーゼ値や心拍変動などの非侵襲的な評価方法が注目されている。申請者は、自律神経系マーカーである唾液アミラーゼ値と心拍変動を同時に測定することにより統合失調症における自律神経機能を詳細に検討した。具体的には、統合失調症患者群・健常成人各25名に対し、唾液アミラーゼ値と心拍変動の同時測定を行った。その結果、心拍変動において交感神経活動指標(LF/HF)は両群間で差は認めなかったが、副交感神経活動指標である高周波成分(HF)では統合失調症群が有意に低下していた。また、唾液アミラーゼ値は、統合失調症患者群で有意に上昇しており、唾液アミラーゼ値と精神症状重症度の間には正の相関を認めた。以上より、統合失調症の唾液アミラーゼ値の上昇の背景には、副交感神経系の機能低下の存在が示唆された。

本研究は統合失調症の病態への自律神経機能異常の関与を強く示唆するものであり、申請者が示した、state markerとしての唾液アミラーゼ値の有用性など、統合失調症の病態把握、さらには発症予防への寄与も考えられる。

最終試験又は学力の確認の結果の要旨

申請者は、統合失調症の精神症状と唾液アミラーゼ値が相関し、その原因として副交感神経活動の低下が関与していることを示した。統合失調症の原因解明と早期診断に寄与する研究と考えられた。関連分野の知識も十分に有し、学位授与に値すると判断した。(主査：田邊一明)

申請者は、統合失調症の診断や病状の程度を判断する非侵襲的かつ簡便な方法として、自律神経系の活動指標となる心拍変動と唾液アミラーゼ含有量に注目し、興味深い知見を得た。本研究は統合失調症の誘発要因の解明や治療法への応用にも繋がり、極めて意義が高い。基本的小および関連する知識も十分にあり、学位授与に値すると判定した。(副査：紫藤 治)

申請者は、非侵襲的測定法を用いて統合失調症の重症度と副交感神経活動や唾液アミラーゼ値の間に有意な相関関係があることを示した。本知見は、統合失調症患者の新しい病状評価法や治療の開発に貢献するものであり、学位授与に値すると判断した。(副査：斉藤洋司)

(備考) 要旨は、それぞれ400字程度とする。