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## Secretagogin may not be a new neuroendocrine biomarker in schizophrenia while levels may reflect clinical severity

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### ABSTRACT

**OBJECTIVE:** Schizophrenia is a neurodegenerative and neurodevelopmental disorder. For this reason, it is important to determine the level of markers that are neuroprotective and have been altered in other neurodegenerative diseases in inspecting the etiology of schizophrenia. Secretagogin (SCGN), is a member of Calcium (Ca) binding proteins and thought to have a neuroprotective effect. In this study, we aimed to compare the level of secretagogin (SCGN) between age and gender-matched schizophrenia and control group.

**METHODS:** Fifty-three patients with schizophrenia who applied to outpatient clinics of our hospital and 37 healthy controls included in the study. Schizophrenia diagnoses of the patients were verified using the DSM-5 criteria. Serum secretagogin levels were measured with the enzyme-linked immunosorbent assay (ELISA) test. The Body Mass Index (BMI) of the patient group was measured.

**RESULTS:** There was no significant difference between the controls and patients in terms of fasting blood glucose and insulin levels. We did not find any difference in terms of the levels of serum secretagogin between patients with schizophrenia and controls. Negative correlations were found between the level of secretagogin and PANSS positive score, PANSS negative score, PANSS general psychopathology score.

**CONCLUSION:** There is increasing evidence that SCGN may play a role in central nervous system (CNS) activity. Future studies might help to explicitly present the relationship between secretagogin and schizophrenia.

### ARTICLE HISTORY

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### KEYWORDS

Schizophrenia;  
neuroendocrine; peripheral  
markers

## Highlights

- We evaluated serum secretagogin levels in patients with schizophrenia.
- No difference was found in terms of the serum secretagogin level between patients with schizophrenia and controls.
- A correlation was found between level of secretagogin and PANSS score.

## 1. Introduction

Schizophrenia is a complex disorder, characterized by molecular, neuroendocrine, and behavioural alterations [1]. Its underlying mechanism has not been completely comprehended yet. Therefore, studies are carried out to understand the pathophysiology of the disease and various comorbidities related to the disease (cardiovascular system, metabolic syndrome) by neuroendocrine, inflammatory, oxidative biomarkers. Use neuroendocrine biomarkers might help measuring

the risk metabolic disorder for patients, understanding the pathophysiological processes associated with schizophrenia and improvement of treatments focused on endocrine and metabolic disorders [2]. Various peripheral biomarker studies have been performed to understand if patients with schizophrenia had more tendency to have metabolic disorder compared to healthy controls. Secretagogin (SCGN) may be one of these biomarkers which could be studied further.

Secretagogin is a member of the EF-hand (E-helix-loop- F-helix-hand) super family of calcium-binding proteins [3,4]. Secretagogin is expressed by a some set of neuronal cells, which are particularly in cerebellum, pituitary gland and hypothalamus [3], and gastrointestinal endocrine cells [4]. Although, the precise physiological role of secretagogin is not known yet, studies in the literature have shown that in addition to transcription and control of insulin secretion [5] and apoptosis [6].

SCGN might be a biomarker for endocrine tumors, stroke, and psychiatric conditions. Secretagogin has

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been hypothetically suggested to have a neuroprotective role in neurodegenerative diseases [7]. Raju et al. was examined the effects of SCGN expression on GABAergic neuron function and form [8]. In schizophrenia, specific subpopulations of GABA neurons have been reported to be severely affected [9–14]. SCGN expression has cell-intrinsic effects on neuronal morphology. Beyond these effects, it is important to recognize that GABA signalling provides excitatory drive for immature neocortical networks. GABA signalling has been also implicated in most aspects of corticogenesis such as proliferation, migration, and synaptogenesis [15]. SCGN's role in cellular defense against neuronal damage, makes it important to investigate in schizophrenia [3,16,17]. For all these reasons, we suggest that SCGN may be associated with psychiatric conditions, especially with schizophrenia. Therefore, in this study, we aimed to evaluate serum secretagogin levels in patients with non-diabetic schizophrenia who had antipsychotic use.

## 2. Material and methods

The patients with schizophrenia who applied to the outpatient unit of Ankara Numune Training and Research Hospital from were included in the study. An ethics committee approval from the our hospital was obtained for the study (Approval date: 2018, Ethic committee number: E-18-1798). We made diagnoses according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria on the basis of a semi-structured clinical interview and it was confirmed after a consensus was established by two of the authors. The control group was selected from health care personnel who did not have any psychiatric diseases. All subjects underwent laboratory tests, including blood lipid panel, fasting blood glucose, C-Reactive Protein (CRP) and insulin. Gender and age of each subject were recorded. Body mass index (BMI) and Homeostasis Model Assessment of Insulin Resistance index (HOMA-IR index) values were noted for each subject. The Positive and Negative Syndrome Scale (PANSS) is applied for each patients with schizophrenia. Alcohol or/and drug use disorder, mental retardation, pregnancy,

previous electroconvulsive therapy (ECT) history, having metabolic disease, previous cerebrovascular event history, malignancy, known inflammatory disease, diabetes mellitus, any pancreatic disease, use of immunosuppressive drug, untreated hypertension and untreated dyslipidemia were regarded as exclusion criteria.

After a night fasting, 5 milliliter (mL) blood was collected from participants and transferred to serum separator tubes. Blood samples were centrifuged at 1.300 g for 10 minutes after clots developed. After serum samples were separated, they were stored at -80 °C (degree Celsius) until they were analysed. Biochemical analyses were performed on these samples. At the same day that the blood samples were collected, PANSS scores were measured for each participant.

### 2.1. Secretagogin study method

Serum Secretagogin levels were measured by commodity ELISA (SunRed, Shanghai Sunred Biological Technology Co., Ltd. Hu Tai Road. Baoshan District. Sanghani, China. REF No: DZE201128379, LOT: 201806) kit. Measurement range was 0,05–15 ng/mL. Sensitivity was 0,042 ng/mL and %CV values were <10%.

### 2.2. Measurements

We collected socio-demographic information on patients with schizophrenia and controls. We did assessment by using the Positive and Negative Syndrome Scale (PANSS) for each patient with schizophrenia. The PANSS is a 30-item rating scale developed by Kay et al. to assess the extent and severity of schizophrenia symptoms. Items were initially compacted to resolve three scales: Positive (7 items), Negative (7 items), and General Psychopathology (GP) (16 items). Trained interviewers administered the PANSS during structured clinical interviews and scored items on a scale from 1 (asymptomatic) to 7 (extremely symptomatic) [18–22]. The validity and reliability of the PANSS's Turkish version were realized by Kostakoğlu et al. [23].

### 2.3. Statistical Analysis

All statistical analyses were performed with IBM SPSS ver.23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). The results were presented as mean ± standard deviation or median (minimum-maximum) for continuous variables. Categorical variables were described as frequency and percentage. Shapiro Wilk test was used as normality test. Continuous variables were compared using Student t-test and Mann-Whitney U test when the data were not normally distributed. Correlations between variables were tested using Pearson and

**Table 1.** Distribution of demographic findings according to patient group and control group.

	Schizophrenia (n = 53)	Controls (n = 37)	p
<b>Gender (Females)</b>	25 (47.2.0%)	16 (43.2%)	0.713
<b>Age</b>	36.09 ± 10.87	33.86 ± 10.86	0.341
<b>Number of hospitalizations</b>	2.84 ± 1.57	NA	–
<b>The duration of disorder</b>	8 (1–28)	NA	–
<b>BMI (kg/m<sup>2</sup>)</b>	24.2 ± 2.00	NA	–

Continuous variables are expressed as mean ± SD or median (min-max). Student's t-test was used.

Categorical variables are expressed as n (%).

NA (not applicable), SD (standard deviation).

**Table 2.** First and second generation antipsychotics in terms of chlorpromazine equivalent doses.

Name of the drug	Number of patients	Median (mg/day)	Minimum (mg/day)	Maximum (mg/day)
Amisulpride [25]	3	200	100	300
Aripiprazole [26]	4	266	200	400
Quetiapine [26]	5	1067	533	1333
Clozapine [24]	6	650	500	1000
Olanzapine [26]	3	400	500	1000
Paliperidone [24]	14	600	400	800
Risperidone [26]	14	400	200	600
Zuclopenthixol [25]	3	200	100	300

Spearman correlation coefficients. A  $p$ -value  $<0.05$  was considered as significant.

### 3. Results

Fifty-three schizophrenia and 37 healthy controls were included in the study. There was no significant difference between the schizophrenia and the control group in terms of age and gender. (see Table 1) 11.3% of the patients with schizophrenia were using first generation antipsychotics (FGAs) and 88.7% of the patients with schizophrenia were using second generation antipsychotics (SGAs). First and second generation antipsychotic doses were calculated according to chlorpromazine equivalent doses (see Table 2) [24–26]; 64.2% of the patients with schizophrenia were smokers.

There was no significant difference between the two groups in terms of serum secretagogin, insulin, HOMA IR and fasting glucose (see Table 3). There was significant difference between the two groups in terms of triglyceride, HDL, VLDL and CRP. Levels of triglyceride, VLDL and CRP in schizophrenia group were found to be higher than in control group (respectively  $p = .015$ ,  $p = .002$ ,  $p = .002$ ). Levels of HDL in schizophrenia group was found to be lower than in control group ( $p = <.001$ ). There was no significant difference between the two groups in terms of serum total cholesterol and LDL (respectively  $p = .066$ ,  $p = .128$ ).

There was no significant difference between the use of first and second group antipsychotics with regard to the level of secretagogin ( $p = .240$ ). There was no difference between the genders in the schizophrenia group and the control group in terms of the secretagogin (respectively  $p = .539$ ,  $p = .540$ ).

There was no correlation between age and the secretagogin in the schizophrenia and control groups (for

**Table 3.** Laboratory findings of schizophrenia and healthy controls groups.

	Schizophrenia ( $n = 53$ )	Controls ( $n = 37$ )	$p$
Secretagogin ( $\mu\text{g/mL}$ )	1.13 (0.55–10.30)	0.96 (0.11–13.15)	0.899
Fasting glucose ( $\text{mg/dL}$ )	89.53 $\pm$ 13.68	91.78 $\pm$ 7.88	0.059
Insulin $\text{mIU/mL}$	10.00 $\pm$ 7.16	10.26 $\pm$ 5.83	0.496
HOMA – IR	1.82 (0.27–13.72)	2.05 (0.34–6.26)	0.452

Continuous variables are expressed as mean  $\pm$  SD.

Student's  $t$ -test was used.

Abbreviations: Homeostasis Model Assessment of Insulin Resistance index (HOMA- IR).

schizophrenia group:  $r = -.213$ ;  $p = 0.127$  for control group:  $r = -.250$ ;  $p = .136$ ). There was no correlation between the duration of hospitalization and the level of the secretagogin in the schizophrenia group ( $r = .034$ ;  $p = .810$ ).

Positive, Negative, and General Psychopathology (GP) scores were calculated in the schizophrenia group (see Table 4). When the correlation between the Spearman correlation coefficient, subscales of secretagogin and PANSS and the PANSS total was evaluated; negative correlation with PANSS positive score ( $r = -.413$   $p = .002$ ), negative correlation with PANSS negative score ( $r = -.801$   $p = .000$ ), negative correlation with PANSS general psychopathology score ( $r = -.576$   $p = .000$ ), negative correlation with PANSS total score ( $r = -.728$   $p = .000$ ) were obtained.

### 4. Discussion

The purpose of this study was to examine the secretagogin protein levels in the serum of patients with schizophrenia compared to healthy controls. In our study, there was no difference in serum secretagogin levels between schizophrenia and control groups. Being the first study investigating the level of secretagogin in patients with schizophrenia having antipsychotic treatment makes this study important. In a previous study, it was found that there were decreased secretagogin levels in schizophrenia post-mortem pituitaries and increased levels of this protein in serum in drug naïve patients with schizophrenia [27]. Distinctly in our study, the change in metabolic parameters was also investigated, however, the previous study examined BMI only.

In the study performed in autism, the level of the secretagogin was found to be lower in severe and mild autism than in controls. In the study performed in autism, the parameters affected by SCGN level such as plasma insulin were not examined [28]. Although, the underlying mechanism of SCGN's action in insulin secretion has not been found yet, SCGN is proposed to enhance secretion of pancreatic insulin; because tissues overexpressing SCGN increases insulin secretion in previous studies [3,5,29]. In our study, there was no difference between the two groups in terms of insulin level. This is a finding that supports the absence of any difference in SCGN level.

In our study, there was a negative correlation between PANSS negative score, PANSS positive score, PANSS general psychopathology score and

**Table 4.** PANSS score to patients with schizophrenia.

	Schizophrenia
PANSS positive score	28.40 $\pm$ 4.19
PANSS negative score	22.04 $\pm$ 7.45
PANSS general psychopathology score	53.55 $\pm$ 10.94
PANSS total score	103.98 $\pm$ 19.08



SCGN. Negative symptoms such as “social withdrawal”, “social functioning disorder” are similar to those in autism. Therefore, the negative correlation between PANSS negative score and SCGN is consistent with the lower SCGN levels in severe and mild autism patients [28]. Positive symptoms include hallucinations, delusions, thought clutter, feelings of grandiosity, skepticism, and hostile attitudes [21]. The general psychopathology scale includes somatic anxiety, anxiety, depression, feelings of guilt, mannerism and body posture, tension, motor deceleration, lack of cooperation, disorientation, unusual thought content, decreased attention, lack of judgment and insight, impulse uncontrol, mental over-occupation and active social avoidance [21]. Attention reduction, lack of cooperation, active social avoidance are common traits of patients with autism and schizophrenia. Besides, the likelihood of positive psychotic symptoms in autism is much higher than in the community. It is thought that SCGN may have a role in cellular defense against neuronal damage [16]. A negative correlation between SCGN and disease severity in the schizophrenia group may be a cause of increased neuronal damage as the disease severity increases.

There is an growing evidence that SCGN may play a role in CNS activity [30]. There are possibilities that SCGN is involved in common basic cellular processes that also affect the nervous system or it may affect certain neurodevelopmental processes directly [28]. Although, the SCGN level was not found to be changed in schizophrenia group of our study, obtaining the negative correlation between the severity of the findings and the level of SCGN may be an indication for future studies to discover possible relationship between schizophrenia and SCGN.

#### 4.1. Limitations

One of the limitations is that number of participants is small. Another important limiting factor is that the control group doesn't have BMI and the schizophrenia group doesn't have a homogenous use of antipsychotic drugs. It is another limitation that the schizophrenia patients without treatment are not included in the study. We also could not compare schizophrenia patients with diabetes or metabolic syndrome and schizophrenia patients without metabolic syndrome or diabetes, which could be listed as a limitation for our study.

#### 5. Conclusion

This study aims to examine SCGN protein level in the plasma of patients with schizophrenia compared to healthy controls. According to our knowledge, this is the first study to investigate the SCGN levels in patients with schizophrenia under treatment. As a result of this study, the levels of SCGN has negative correlation with

total PANSS score of patients with schizophrenia. These results may show us, SCGN may affect particular neurodegenerative processes. But we need new studies for saying that. Future studies conducted on SCGN levels of schizophrenia groups with metabolic parameter deterioration might help us understand the effect SCGN has on schizophrenia patients.

#### Disclosure Statement

No potential conflict of interest was reported by the authors.

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