Neuroendocrinology Letters Volume 44 No. 6 2023
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

ORIGINAL ARTICLE

Higher concentration in serum of insulin autoantibodies in patients with schizophrenia or related psychosis, compared to in control subjects.

Kristina Melkersson[1], Sophie Bensing[1,2]

1 Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden.
2 Department of Endocrinology, Karolinska University Hospital, Stockholm, Sweden.

Correspondence to: Kristina Melkersson, MD, PhD
Department of Molecular Medicine and Surgery, Karolinska Institutet,
Old Karolinska University Hospital Solna, L1:00, SE-171 76 Stockholm, Sweden
e-mail: Kristina.Melkersson@ki.se

Submitted: 2023-06-19 Accepted: 2023-08-14 Published online: 2023-08-16

Key words: **schizophrenia; autoantibodies; NMDAR; VGKC; AMPAR; $GABA_BR$; DPPX; GAD; IA-2; ZnT8; insulin; VGCC**

Neuroendocrinol Lett 2023; **44**(6):358–367 **PMID:** 37776553 NEL440623A02 © 2023 Neuroendocrinology Letters • **www.nel.edu**

Abstract

OBJECTIVES: In a recent study, we found increased antibody reactivity against the insulin receptor-A and insulin-like growth factor 1 receptor and their ligands in patients with schizophrenia or related psychosis, indicating that an autoimmune-mediated process may underlie development of schizophrenia. The aim of this study was to supplement our previous study with analysing additional neuronal- and diabetes-associated autoantibodies of potential interest for schizophrenia in the same patients and controls as in the foregoing study.
MATERIAL AND METHODS: Analyses of neuronal (NMDAR, VGKC, AMPAR, $GABA_BR$, DPPX, GAD)- and voltage-gated calcium channel (VGCC) autoantibodies in cerebrospinal fluid (12 patients, 11 controls) and of diabetes-associated (GAD, IA-2, ZnT8, insulin)- and VGCC autoantibodies in serum (17 patients, 11 controls) were done by standard methods. Additionally, patients (n = 16) were accessed for clinical symptoms with the Positive and Negative Syndrome Scale (PANSS) for schizophrenia.
RESULTS: Concentrations in cerebrospinal fluid of NMDAR-, VGKC-, AMPAR-, $GABA_BR$-, DPPX-, GAD- and VGCC autoantibodies were below detection limits in all patients and controls. Concentration in serum of insulin autoantibodies was significantly higher in patients than in controls ($p = 0.001$), whereas no significant differences were found in concentrations in serum of GAD-, IA-2-, ZnT8- or VGCC autoantibodies between patients and controls. Patients' serum concentrations of insulin autoantibodies tended to inversely correlate to their PANSS scores.
CONCLUSION: In this study, we show higher concentration in serum of insulin autoantibodies in patients with schizophrenia. This finding is of importance since autoantibodies against insulin may be implicated in the autoimmune-mediated process underlying development of schizophrenia.

Abbreviations:

AMPAR	- α-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid receptor
CASPR2	- contactin-associated protein 2
C-peptide	- connecting-peptide
CSF	- cerebrospinal fluid
DPPX	- dipeptidyl-peptidase-like protein-6
$GABA_BR$	- γ-amino-butyric acid B-receptor
GAD	- glutamic acid decarboxylase
IA-2	- islet antigen-2
IGF1	- insulin-like growth factor 1
IGF1R	- insulin-like growth factor 1 receptor
IgG	- immunoglobulin G
Ins	- insulin
INSR-A	- insulin receptor-A
LGI1 protein	- leucine-rich glioma-inactivated 1 protein
NMDAR	- *N*-methyl-D-aspartate receptor
PANSS	- positive and negative syndrome scale
r_s	- Spearman rank correlation coefficient
VGCC	- voltage-gated calcium channel
VGKC	- voltage-gated potassium channel
ZnT8	- zinc transporter 8

INTRODUCTION

Schizophrenia is a psychotic disorder that affects approximately 0.5% of the population worldwide (Charlson *et al.* 2018; McGrath *et al.* 2008). In general it is disabling with a chronic course, beginning in late adolescence or early adulthood and continuing throughout life (Freedman, 2003). The literature provides strong evidence for a role of genetic factors in its aetiology (Craddock *et al.* 2005), and of all 287 schizophrenia-associated genetic risk loci identified to date, it is the gene region encompassing the major histocompatibility complex on chromosome 6p22.1 playing an important role in the immune system that is the most significant and consistent, followed by genes involved in calcium ion import into cells, cell membrane depolarization during action potential, and synaptic transmission (Hall *et al.* 2020; Pardiňas *et al.* 2018; Ripke *et al.* 2014; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2022; Sekar *et al.* 2016). However, a substantial proportion of the heritability for schizophrenia is still unknown (Pardiňas *et al.* 2018; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2022).

Over the years, evidence has accumulated indicating that schizophrenia is a systemic disorder and not only a brain disease (Flyckt, 2001; Kirkpatrick *et al.* 2014; Moises *et al.* 2002), and that an inflammatory, probably autoimmune-mediated, process in the central nervous system and to some extent in peripheral organs, combined with an aberrant immune system, may underlie the development of schizophrenia, at least in a subgroup of patients (Al-Diwani *et al.* 2017; Bejerot *et al.* 2023; Bergink *et al.* 2014; Braun *et al.* 2017; Endres *et al.* 2022; Ermakov *et al.* 2017; Horváth & Mirnics, 2014; Hwang *et al.* 2013; Jeppesen & Eriksen Benros, 2019; Johansson *et al.* 2012; Laskaris *et al.* 2016; Mané-Damas *et al.* 2019; Melkersson & Bensing, 2018, 2021; Miller *et al.* 2011; Mobarrez *et al.* 2013; Momtazmanesh *et al.* 2019; Mongan *et al.* 2020; Müller *et al.* 2000; Schlaaff *et al.* 2020; Schmitt *et al.* 2011; Schwarz *et al.* 2000; Trépanier *et al.* 2016; Upthegrove *et al.* 2014; van Mierlo *et al.* 2019; Wang *et al.* 2018; Wetterberg *et al.* 2002). The aberrance of the immune system in schizophrenia includes reduced capacity of both the cellular and humoral immune responses, as patients with schizophrenia exhibit both a decreased cutaneous cellular immune response to stimulation with a foreign protein or tuberculin, and a reduced antibody production after, for example, vaccination with a salmonella antigen (Melkersson, 2013; Melkersson & Bensing, 2018; Molholm, 1942; Müller *et al.* 1991, 2000; Steiner *et al.* 2010; Özek *et al.* 1971).

Autoantibodies directed against brain tissue, blood cells, heat shock proteins, nerve growth factor and *N*-methyl-D-aspartate receptor (NMDAR) have previously been detected in serum of patients with schizophrenia (Abramson, 1967; Ebert *et al.* 2013; Kagami *et al.* 1987; Kilidireas *et al.* 1992; Kim *et al.* 2001; Klyushnik *et al.* 1999; Lennox *et al.* 2017; Popova, 1977; Schwarz *et al.* 1998, 1999; Shcherbakova *et al.* 2004; Shinitzky *et al.* 1991; Spivak *et al.* 2009a, 2009b; Steiner *et al.* 2013; Tong *et al.* 2019; Wang *et al.* 2003).

Furthermore, we recently found increased antibody reactivity against the insulin receptor-A (INSR-A) and insulin-like growth factor 1 receptor (IGF1R) and their ligands connecting (C)-peptide, insulin (Ins) and insulin-like growth factor 1 (IGF1) in cerebrospinal fluid (CSF) and serum of patients with schizophrenia or related psychosis (Melkersson & Bensing, 2021). However, in that study, no (or only partial) analyses were done regarding additional neuronal- and diabetes-associated autoantibodies, which also may be of potential interest in the development of schizophrenia (Bingley, 2010; Dalmau & Rosenfeld, 2008; Leypoldt *et al.* 2015; Pozzilli *et al.* 2001). Therefore, we aimed in this study to supplement our earlier study (Melkersson & Bensing, 2021) by analysing these antibodies in CSF and/ or serum from the same patients with schizophrenia or related psychosis and control subjects as in the foregoing study.

MATERIAL AND METHODS

Ethical approval

The study was approved by The Ethics Committee of Karolinska Institutet and The Regional Ethical Review Board, Stockholm, Sweden, and all patients and control subjects participated after giving informed consent.

Patients and control subjects

Consecutive outpatients at psychiatric polyclinics in the region of Stockholm, Sweden, diagnosed with schizophrenia or schizoaffective disorder according to Diagnostic and statistical manual of mental disorders (5th edition) criteria (American Psychiatric Association,

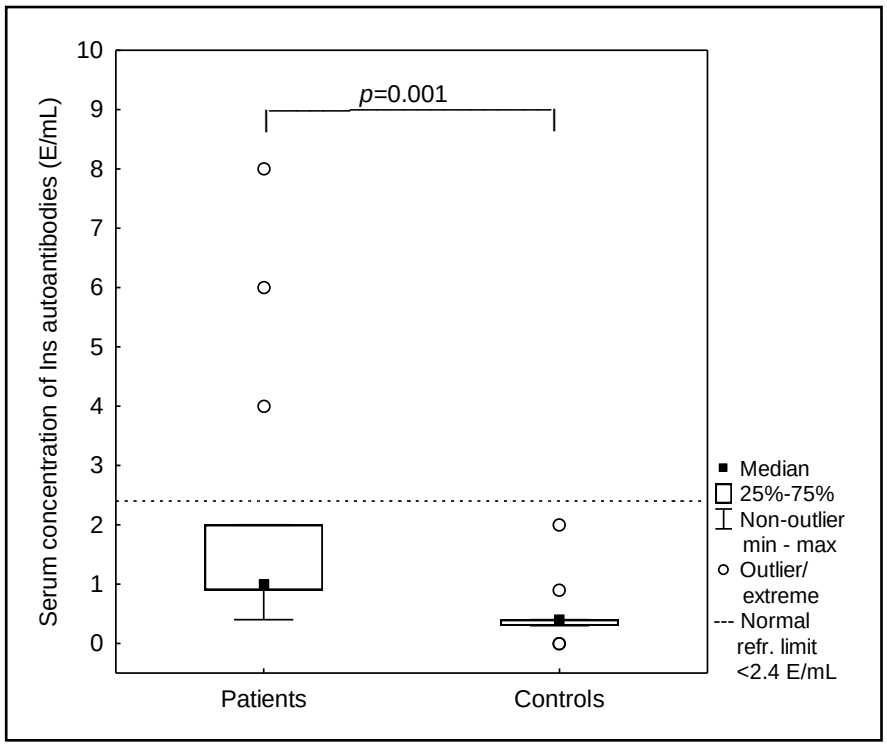

Fig. 1. Median (range) serum concentration of insulin (Ins) autoantibodies in patients with schizophrenia or related psychosis (n=17), compared with that in controls (n=9), 1.0 (0.4-8.0) versus 0.4 (0.0-2.0) E/mL, p=0.001.

2013), were invited to participate in this study. Any patients having a substance-related disorder or a physical illness that could influence the evaluation were excluded. In total, 17 patients were included. In addition, 11 individuals diagnosed with non-inflammatory neurological diseases were included as control subjects.

Characteristics of the patients and control subjects are given in Table 1. All patients were Caucasians and had a diagnosis of schizophrenia, except one woman who was diagnosed with schizoaffective disorder. Nine (52.9%) of the patients had heredity for schizophrenia or related psychosis, and twelve (70.6%) of the patients had heredity for diabetes mellitus type 1, type 2 or both types (Melkersson, 2009; Table 1). None (0.0%) of the male patients compared to seven (70.0%) of the female patients were smokers (p = 0.010), otherwise no sex differences in characteristics were found among the patients. Male and female patients were also treated with similar antipsychotics, and the only concomitant medications used were benzodiazepine derivatives (n = 3), lithium (n = 1), orphenadrine (n = 1), propiomazine (n = 1), zopiclon (n = 1) and zopiderm (n = 1). The control subjects were all Caucasians except one woman who was Asian, and none had any diagnosis of psychotic disorder; neither did they use any drugs with anti-inflammatory effect that could influence their neurological disease, such as cortisone, interferon or cytostatics.

Clinical evaluation and laboratory analyses

The clinical evaluation of the patients was done by a psychiatrist on the day before the taking of CSF and serum specimens by using the Positive and Negative Syndrome Scale (PANSS) for schizophrenia (Kay *et al.* 1987; Von Knorring & Lindström, 1992). The PANSS consists of four subscales of symptom complexes (positive symptoms, negative symptoms, positive and negative symptoms combined, and general psychiatric symptoms), each of the items is rated on different point scales.

The lumbar punctures and collections of blood samples were carried out in the morning after the patients and control subjects had been fasting overnight, and the CSF and serum samples were frozen directly and stored in -80°C until analysis. Serum samples were then diluted 1:100 for the analyses of glutamic acid decarboxylase (GAD)- and Ins autoantibodies, otherwise undiluted samples of CSF and serum were used in the analyses. Cerebrospinal fluid from 12 patients and 11 control subjects were analysed for neuronal NMDAR-, voltage-gated potassium channel (VGKC; leucine-rich glioma-inactivated 1 (LGI1) protein, contactin-associated protein 2 (CASPR2))-, α-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid receptor (AMPAR)-, γ-amino-butyric acid B-receptor ($GABA_BR$)- and dipeptidyl-peptidase-like protein-6 (DPPX) immunoglobulin G (IgG)-autoantibodies by an immunofluorescence assay according to the guidelines of the manufacturer (Euroimmun AG, Luebeck, Germany), and for neuronal GAD autoantibody by a GAD Autoantibody ELISA kit (RSR Limited, Cardiff, United Kingdom). Serum from 17 patients and 11 control subjects were analysed for diabetes-associated (GAD-, zinc transporter 8 (ZnT8)-, islet antigen-2 (IA-2)- and Ins) autoantibodies by

Tab. 1. Characteristics of the patients and control subjects

	Ethnicity, n	Age[a], y	Smoking, n (%)	Diagnosis, n	Heredity for schizophrenia or related psychosis[b], n (%)	Heredity for diabetes mellitus[c], n (%)	Duration of psychotic disorder[a], y	Type of current antipsychotic, n	Treatment time with current antipsychotic[a], y
Patients (n=17; 7 men, 10 women)	Caucasian (n=17)	44 (26-58)	7 (41.2)	Schizophrenia[d] (n=16) Schizoaffective disorder[d] (n=1)	9 (52.9)	type 1: 1 (5.9) type 2: 9 (52.9) both types: 2 (11.8)	17.0 (3.0-35.0)	Haloperidol (n=1) Clozapine (n=3) Olanzapine (n=6) Perphenazine (n=1) Risperidone (n=5) Zuclopentixol (n=1)	5.0 (1.0-14.4)[e]
Control subjects (n=11; 3 men, 8 women)	Caucasian (n=10) Asian (n=1)	44 (28-55)	nda	Non-inflammatory neurological disease[f] (n=11)	nda	nda	na	na	na

Abbreviations: n=number, na=not applicable, nda=no data available, y=year
[a] The data are given as median and range
[b] I.e. patients who had one or more first-, second-, third- or fourth-degree relatives (excluding siblings) with schizophrenia or related psychosis (Melkersson, 2009)
[c] I.e. patients who had one or more first-, second-, third- or fourth-degree relatives (excluding siblings) with diabetes mellitus type 1, type 2 or both types (Melkersson, 2009)
[d] According to Diagnostic and statistical manual of mental disorders (5th edition) criteria (American Psychiatric Association, 2013)
[e] 1 missing value
[f] In the foregoing study (Melkersson & Bensing, 2021), one of the 12 primary controls was found to have increased antibody reactivity against the calcium-activated chloride-channel protein fragment anoctamin 2_HPRR3070036 that is identified as an autoimmune target in multiple sclerosis, and was therefore excluded as control also in this study

commercial GAD-, ZnT8- and IA-2 Autoantibody ELISA kits (RSR Limited, Cardiff, United Kingdom) and an enzymimmunoassay for determination of Ins autoantibody (Medizym® IAA, Medipan GMBH, Berlin, Germany). All these autoantibody analyses were conducted at the Department of Clinical Immunology, Karolinska University Laboratory, Solna, Sweden. In addition, analysis of the voltage-gated calcium channel (VGCC, P/Q-type) autoantibody was done in CSF from 12 patients and 11 control subjects and in serum from 17 patients and 11 control subjects by a radioimmunopercipitation method at Wieslab AB, Malmö, Sweden. The detection limits for the analyses of autoantibodies were titre ≥1 for NMDAR, VGKC (LGI1, CASPR2), AMPAR, $GABA_BR$ and DPPX in CSF, ≥5 IE/mL for GAD in CSF and serum, ≥8 IE/mL for IA-2 in serum, ≥2 E/mL for ZnT8 in serum, ≥0.3 E/mL for Ins in serum, and ≥1.00 pmol/L for VGCC in CSF and serum.

Statistical methods

The continuous data age, duration of psychotic disorder, treatment time with current antipsychotic and PANSS scores are given as median and range, and the categorical data smoking, heredity for schizophrenia or related psychosis and heredity for diabetes mellitus type 1, type 2 or both types are summarized using frequency counts and percentages. Comparisons between all patients and control subjects, or between subgroups of patients, were conducted with Mann-Whitney test or Fisher's exact test. To measure the correlation between pairs of variables, Spearman rank correlation coefficient (r_s) was calculated. A p-value of less than 0.05 was considered statistically significant. All calculations were done with the statistical program Statistica for Windows 13.5 (TIBCO Software Inc., Palo Alto, CA, USA).

RESULTS

The concentrations in CSF of NMDAR-, VGKC (LGI1, CASPR2)-, AMPAR-, $GABA_BR$-, DPPX-, GAD- and VGCC (P/Q-type) autoantibodies were below detection limits in all patients (n = 12) and control subjects (n = 11). Added to this, the concentration in serum of VGCC (P/Q-type) autoantibodies was below normal reference limit (i.e. <40 pmol/L) in all patients (n = 17) and control subjects (n = 11).

Median (range) concentration in serum of Ins autoantibodies was significantly higher in patients than in control subjects (1.0 (0.4-8.0) versus 0.4 (0.0-2.0) E/mL, p = 0.001; Figure 1), whereas no significant differences were found in median concentrations in serum of ZnT8-, GAD- or IA-2 autoantibodies between patients and control subjects. However, increased concentrations in serum of Ins-, ZnT8-, GAD- or IA-2 autoantibodies

Tab. 2. Scores obtained with the Positive and Negative Syndrome Scale (PANSS) for schizophrenia in the patients studied [a]

	PANSS scores			
	Positive symptoms	**Negative symptoms**	**Positive and negative symptoms combined**	**General psychiatric symptoms**
Median (range)	10.0 (7.0-17.0)	9.0 (7.0-12.0)	1.0 (-5.0-9.0)	21.0 (16.0-26.0)
Reference range[b]	7-49	7-49	-42-42	16-112

[a] n=16 due to missing PANSS data in 1 patient
[b] According to Kay *et al.* 1987

were not more prevalent in patients than in control subjects. Three (17.7%) of 17 patients versus 0 (0.0%) of 9 control subjects had increased serum concentration of Ins autoantibodies, i.e. ≥2.4 E/mL (p = 0.529), and 2 (11.8%) of 17 patients versus 0 (0.0%) of 9 control subjects had increased serum concentration of ZnT8 autoantibodies, i.e. ≥15 E/mL (p = 0.529). It was two 46- and 58-year-old women diagnosed with schizophrenia but otherwise healthy, who had increased serum concentration of Ins autoantibodies (4.0 and 8.0 E/mL, respectively), and one 39-year-old woman diagnosed with schizoaffective disorder but otherwise healthy, who had increased serum concentrations of both Ins- and ZnT8 autoantibodies (6.0 and 18 E/mL, respectively). The fourth patient was a 50-year-old woman diagnosed with schizophrenia and rheumatoid arthritis but otherwise healthy, who had increased serum concentration of solely ZnT8 autoantibodies (38 E/mL). Moreover, 1 (5.9%) of 17 patients versus 0 (0.0%) of 9 control subjects had increased serum concentrations of GAD- and IA-2 autoantibodies, i.e. ≥5 and ≥8 IE/mL, respectively (p = 1.000). This patient was a 54-year-old woman diagnosed with schizophrenia but otherwise healthy, who had increased serum concentrations of both GAD- and IA-2 autoantibodies (>250 and 49 IE/mL, respectively).

Median and range of PANSS scores in patients (n = 16) are given in Table 2. Patients' serum concentrations of Ins autoantibodies tended to inversely correlate to their PANSS scores of positive symptoms (r_s = -0.43, p = 0.099), and of positive and negative symptoms combined (r_s = -0.45, p = 0.079). Moreover, subgroup analysis showed that patients' serum concentrations of Ins autoantibodies tended to associate to heredity for diabetes mellitus type 1 in that there was a tendency towards that more patients with than without heredity for diabetes mellitus type 1 had increased serum concentration of Ins autoantibodies (2/3 (66.7%) versus 1/14 (7.1%), p = 0.063). However, subgroup analyses of patients' serum concentrations of Ins autoantibodies in relation to sex, smoking, full or partial symptom remission, heredity for schizophrenia or related psychosis, or heredity for diabetes mellitus type 2 did not show any tendencies towards significant, or significant associations.

DISCUSSION

In this study, we show higher serum concentration of autoantibodies directed against Ins in patients with schizophrenia or related psychosis, compared with control subjects. The serum concentrations of Ins autoantibodies in the patients tended also to inversely correlate to their PANSS scores of positive symptoms, and of positive and negative symptoms combined, telling us that higher concentration of Ins antibodies in serum may constitute a remission marker in schizophrenia. The results are in several parts, although not fully, in accord with the findings in our foregoing study, showing increased antibody reactivity in serum from the same patients as in this study against Ins peptides no´s 1, 6, 7 and 9 (i.e. a part of Ins ß-chain, C-peptide, and a part of Ins α-chain) (Melkersson & Bensing, 2021). In the foregoing study, we also found an inverse correlation between patients' antibody reactivity in serum against Ins peptide no. 2 (i.e. a part of Ins ß-chain) and their PANSS scores of negative symptoms, but no tendencies towards significant, or significant correlations between patients' antibody reactivity in serum against Ins peptides no´s 1, 6, 7 or 9 and their PANSS scores (Melkersson & Bensing, 2021). The minor discrepancíes in results between the two studies may to a great extent be explained by the use of different analysis methods; in the foregoing study, we analysed the antibody reactivity in serum directed against both Ins (Ins peptides no´s 1-2 and 8-9) and C-peptide (Ins peptides no´s 3-7) by using a peptide antigen bead array designed by ourselves (Melkersson & Bensing, 2021), whereas in this study, we analysed the concentration of Ins autoantibodies in serum by using the commercial enzymimmunoassay Medizym® IAA that specifically analyses autoantibodies directed against Ins, but not against C-peptide (Medipan GMBH, Berlin, Germany, personal communication). In comparison with others' studies, the only earlier study published shows, as this study, no differences in plasma levels of IgG against GAD and IA-2a (= IA-2), but decreased plasma levels of IgG against, not analysed by us, IA-2b, in patients with schizophrenia, compared with control subjects (Hallford *et al.* 2016). However, plasma or serum levels of autoantibodies directed against Ins and C-peptide were not analysed in their study (Hallford *et al.* 2016).

One of the patients with a diagnosis of schizophrenia but otherwise healthy, had increased concentration of GAD autoantibodies in serum, but not in CSF, indicating no presence of autoimmune GAD encephalitis, but an increased risk for future development of diabetes mellitus type 1, especially as the patient had increased concentration of IA-2 diabetes-associated autoantibodies in serum too (Bingley, 2010; Graus *et al.* 2016; Krischer *et al.* 2015; Pozzilli *et al.* 2001). This patient had also heredity for both schizophrenia or related psychosis and diabetes mellitus type 2, however, not for diabetes mellitus type 1.

Neuronal NMDAR-, VGKC (LGI1, CASPR2)-, AMPAR-, $GABA_BR$-, DPPX- and GAD autoantibodies were not detected in CSF of the patients with schizophrenia or related psychosis in this study, supporting the notion that these neuronal autoantibodies do not usually occur in patients with schizophrenia, and if found in this group of patients, it deals in most of all cases with rare cases presenting as schizophrenia-like psychosis (Bien *et al.* 2021; Dalmau, 2016; Endres *et al.* 2015, 2020; Grain *et al.* 2017; Guasp *et al.* 2021; Hansen *et al.* 2022; Haussleiter *et al.* 2017; Najjar *et al.* 2012; Oviedo-Salcedo *et al.* 2018; Theorell *et al.* 2021; Vitaliani *et al.* 2005; Zandi *et al.* 2011).

Over the years, *in vitro*, clinical and genetic findings related to alterations of the intracellular calcium homeostasis have been reported in schizophrenia (Bojarski *et al.* 2010; Giegling *et al.* 2010; Melkersson, 2010). It is also well established that calcium plays an important role in the release of neurotransmitters and hormones in the central nervous system, as well as peripherally, in for example the release of Ins from pancreatic ß-cells (McClenaghan & Flatt, 1999; Melkersson, 2010; Rubin, 1970). However, increased concentrations of autoantibodies directed against the VGCC-complex were not found in CSF and serum of the patients with schizophrenia or related psychosis in this study, supporting the notion that autoantibodies directed against VGCCs, which are the main conduit for calcium entry into many cells, do not explain the pathogenesis of schizophrenia (Gupta *et al.* 2009; Liao & Soong, 2010).

Insulin receptor-A is present in both the central nervous system and peripheral organs, while insulin receptor-B is present only in peripheral organs, in humans (Moller *et al.* 1989; Mosthaf *et al.* 1990; Sara *et al.* 1982; Schulingkamp *et al.* 2000; Sesti *et al.* 1994), leaving INSR-A as being the INSR isoform of main interest in schizophrenia. Insulin as well is present in the central nervous system (Baskin *et al.* 1987; Kullman *et al.* 2016), where it is suggested to have neuromodulatory functions and also to be of relevance to various aspects of the pathophysiology of schizophrenia, including the regulation of dopamine levels (Agarwal *et al.* 2020; de Bartolomeis *et al.* 2023). Insulin has also been demonstrated to both inhibit [^{3}H] norepinephrine uptake and stimulate [^{3}H] serotonin uptake in neuronal cells *in vitro* (Boyd *et al.* 1985). In 1983, Ins autoantibodies were described for the first time in serum of children with newly-diagnosed untreated diabetes mellitus type 1 (Palmer *et al.* 1983). Today, Ins autoantibodies in serum constitute one of several autoantibody markers for diabetes mellitus type 1 (Bingley, 2010; Krischer *et al.* 2015; Pozzilli *et al.* 2001). However, Ins autoantibodies in serum have been found not to be completely specific to diabetes mellitus type 1, as they also may occur, albeit rarely, in autoimmune thyroid diseases and drug-induced autoimmune syndromes (Benson *et al.* 1985; Hegewald *et al.* 1992; Uchigata *et al.* 1994; Wilkin, 1991). The finding of higher concentration of Ins autoantibodies in serum of patients with schizophrenia or related psychosis in this study is in line with a) our previously-described hypothesis that impaired cellular signalling via the INSR-A, and probably also via the IGF1R, may underlie known abnormalities in the central nervous system and peripheral organs in schizophrenia (Melkersson & Persson, 2011, 2012; Melkersson *et al.* 2011), b) results in our foregoing study, indicating that an autoimmune-mediated process underlies the development of a core group of schizophrenia cases and that the INSR-A and IGF1R and their ligands Ins, C-peptide and IGF1 may constitute main antigen targets (Melkersson & Bensing, 2021), and c) are also supported by several studies by others, reporting INSR deficits and decreased IGF1R-, IGF1- and insulin-like growth factor binding protein 2 mRNA expression in post-mortem brains, Ins-signalling abnormalities, altered insulin-like growth factor 2 signalling, and association between an insulin receptor substrate-2 SNP and auditory hallucinations in patients with schizophrenia (Kapogiannis *et al.* 2019; Kim *et al.* 2013; van Beveren *et al.* 2014; Weissleder *et al.* 2021; Wu *et al.* 2013; Yang *et al.* 2020; Zhao *et al.* 2006).

The strength of this study includes the narrow diagnostic selection of, in the main, only patients with a diagnosis of schizophrenia, allowing investigation of a diagnostically homogeneous patient group. The limitations of the study, on the other hand, consist of its limited sample size not large enough to achieve sufficient power in some of the statistical analyses, and the fact that the patients were on antipsychotic drug treatment and were not acutely psychotic, which may have moderated the antibody concentrations observed (Ezeoke *et al.* 2013; Jernbom Falk *et al.* 2021; Ponsford *et al.* 2019). The limitations also include that the control group in this study did not comprise healthy individuals. However, it seems unlikely that the control group selected, in which all control subjects were diagnosed with solely non-inflammatory neurological diseases and did not have any diagnosis of psychotic disorder, can have confounded our results.

To conclude, we show in this study higher concentration in serum of autoantibodies directed against Ins in patients with schizophrenia or related psychosis, compared with control subjects. We also show that higher concentration of Ins autoantibodies in serum

may constitute a remission marker in schizophrenia. Moreover, we do not find evidence that the neuronal (NMDAR, VGKC (LGI1, CASPR-2), AMPAR, $GABA_BR$ and DPPX)-, VGCC- and other diabetes-associated (GAD, ZnT8 and IA-2) autoantibodies play a role in the development of schizophrenia. These findings will bring some important pieces into (as well leave out some others from) the schizophrenia-aetiology puzzle.

ACKNOWLEDGEMENTS

This study was supported by grants from the Foundation Tornspiran (K.M.). We also thank Professor in Neurology Tomas Olsson at Karolinska Institutet, Stockholm, Sweden for the contribution of control subjects to the study, and the Department of Clinical Immunology, Karolinska University Laboratory, Solna, Sweden for professionally conducted autoantibody assessments.

REFERENCES

1 Abramson HA (1967). Schizophrenic sera contain antibody against brain [review]. J Asthma Res. **4**: 229–231.
2 Agarwal SM, Caravaggio F, Costa-Dookhan KA, Castellani L, Kowalchuk C, Asgariroozbehani R, et al. (2020). Brain insulin action in schizophrenia: something borrowed and something new [review]. Neuropharmacology. **163**: 107633.
3 Al-Diwani AAJ, Pollak TA, Irani SR, Lennox BR (2017). Psychosis: an autoimmune disease [review]? Immunology. **152**: 388–401.
4 American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders, 5th ed. Arlington, VA, USA: American Psychiatric Publishing.
5 Baskin DG, Figlewicz DP, Woods SC, Porte D, Dorsa DM (1987). Insulin in the brain [review]. Ann Rev Physiol. **49**: 335–347.
6 Bejerot S, Sigra Stein S, Welin E, Eklund D, Hylén U, Humble MB (2023). Rituximab as an adjunctive treatment for schizophrenia spectrum disorder or obsessive-compulsive disorder: Two open-label pilot studies on treatment-resistant patients. J Psychiatr Res. **158**: 319–329.
7 Benson EA, Healey LA, Barron EJ (1985). Insulin antibodies in patients receiving penicillamine. Am J Med. **78**: 857–860.
8 Bergink V, Gibney SM, Drexhage HA (2014). Autoimmunity, inflammation, and psychosis: a search for peripheral markers [review]. Biol Psychiatry. **75**: 324–331.
9 Bien CG, Rohleder C, Mueller JK, Bien CI, Koethe D, Leweke FM (2021). Neural autoantibodies in cerebrospinal fluid and serum in clinical high risk for psychosis, first-episode psychosis, and healthy volunteers. Front Psychiatry. **12**: 654602.
10 Bingley PJ (2010). Clinical applications of diabetes antibody testing [review]. J Clin Endocrinol Metab. **95**: 25–33.
11 Bojarski L, Debowska K, Wojda U (2010). In vitro findings of alterations in intracellular calcium homeostasis in schizophrenia [review]. Prog Neuropsychopharmacol Biol Psychiatry. **34**: 1367–1374.
12 Boyd FT, Clarke DW, Muther TF, Raizada MK (1985). Insulin receptors and insulin modulation of norepinephrine uptake in neuronal cultures from rat brain. J Biol Chem. **260**: 15880–15884.
13 Braun S, Bridler R, Müller N, Schwarz MJ, Seifritz E, Weisbrod M, et al. (2017). Inflammatory processes and schizophrenia: two independent lines of evidence from a study of twins discordant and concordant for schizophrenic disorders. Eur Arch Psychiatry Clin Neurosci. **267**: 377–389.
14 Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, et al. (2018). Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. Schizophr Bull. **44**: 1195–1203.
15 Craddock N, O'Donovan MC, Owen MJ (2005). The genetics of schizophrenia and bipolar disorder: dissecting psychosis [review]. J Med Genet. **42**: 193–204.
16 Dalmau J (2016). NMDA receptor encephalitis and other antibody-mediated disorders of the synapse. The 2016 Cotzias Lecture. Neurology. **87**: 2471–2482.
17 Dalmau J, Rosenfeld MR (2008). Paraneoplastic syndromes of the CNS [review]. Lancet Neurol. **7**: 327–340.
18 de Bartolomeis A, De Simone G, De Prisco M, Barone A, Napoli R, Beguinot F, et al. (2023). Insulin effects on core neurotransmitter pathways involved in schizophrenia neurobiology: a meta-analysis of preclinical studies. Implications for the treatment [review]. Mol Psychiatry. https://doi.org/10.1038/s41380-023-02065-4.
19 Ebert T, Schechtman M, Ram A, Kosov I, Weizman A, Shinitzky M, et al. (2013). High circulatory titer of platelet-associated autoantibodies in childhood onset schizophrenia and its diagnostic implications. Neuropsychobiology. **68**: 124–127.
20 Endres D, Matysik M, Feige B, Venhoff N, Schweizer T, Michel M, et al. (2020). Diagnosing organic causes of schizophrenia spectrum disorders: findings from a one-year cohort of the Freiburg diagnostic protocol in psychosis (FDPP). Diagnostics. **10**: 691.
21 Endres D, Perlov E, Baumgartner A, Hottenrott T, Dersch R, Stich O, et al. (2015). Immunological findings in psychotic syndromes: a tertiary care hospital's CSF sample of 180 patients. Front Hum Neurosci. **9**: 476.
22 Endres D, von Zedtwitz K, Matteit I, Bünger I, Foverskov-Rasmussen H, Runge K, et al. (2022). Spectrum of novel anti-central nervous system autoantibodies in the cerebrospinal fluid of 119 patients with schizophreniform and affective disorders. Biol Psychiatry. **92**: 261–274.
23 Ermakov EA, Smirnova LP, Bokhan NA, Semke AV, Ivanova SA, Buneva VN, et al. (2017). Catalase activity of IgG antibodies from the sera of healthy donors and patients with schizophrenia. PLoS ONE. **12**: e0183867.
24 Ezeoke A, Mellor A, Buckley P, Miller B (2013). A systematic, quantitative review of blood autoantibodies in schizophrenia. Schizophr Res. **150**: 245–251.
25 Flyckt L (2001). Schizophrenia as a systemic disorder – studies of peripheral and central biological functions [dissertation]. Stockholm, Sweden: Karolinska Institutet.
26 Freedman R (2003). Schizophrenia [review]. N Engl J Med. **349**: 1738–1749.
27 Giegling I, Genius J, Benninghoff J, Rujescu D (2010). Genetic findings in schizophrenia patients related to alterations in the intracellular Ca-homeostasis [review]. Prog Neuropsychopharmacol Biol Psychiatry. **34**: 1375–1380.
28 Grain R, Lally J, Stubbs B, Malik S, LeMince A, Nicholson TR, et al. (2017). Autoantibodies against voltage-gated potassium channel (VGKC) and glutamic acid decarboxylase (GAD) in psychosis: a systematic review, meta-analysis and case series. Psychiatry Clin Neurosci. **71**: 678–689.
29 Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. (2016). A clinical approach to diagnosis of autoimmune encephalitis [review]. Lancet Neurol. **15**: 391–404.
30 Guasp M, Giné-Servén E, Maudes E, Rosa-Justicia M, Martinez-Hernández E, Boix-Quintana E, et al. (2021). Clinical, neuroimmunologic, and CSF investigations in first episode psychosis. Neurology. **97**: e61–e75.
31 Gupta S, Salam N, Srivastava V, Singla R, Behera D, Khayyam KU, et al. (2009). Voltage gated calcium channels negatively regulate protective immunity to Mycobacterium tuberculosis. PLoS ONE. **4**: e5305.
32 Hall LS, Medway CW, Pain O, Pardiñas AF, Rees EG, Escott-Price V, et al. (2020). A transcriptome-wide association study implicates specific pre- and post-synaptic abnormalities in schizophrenia. Hum Mol Genet. **29**: 159–167.
33 Hallford P, St Clair D, Halley L, Mustard C, Wei J (2016). A study of type-1 diabetes associated autoantibodies in schizophrenia. Schizophr Res. **176**: 186–190.
34 Hansen N, Bartels C, Teegen B, Wiltfang J, Malchow B (2022). Catatonic schizophrenia associated with cerebrospinal GAD65 autoantibodies: case report and literature review. Front Immunol. **13**: 829058.

35 Haussleiter IS, Wandinger K-P, Juckel G (2017). A case of GABAR antibodies in schizophrenia. BMC Psychiatry. **17**: 9.
36 Hegewald MJ, Schoenfeld SL, McCulloch DK, Greenbaum CJ, Klaff LJ, Palmer JP (1992). Increased specificity and sensitivity of insulin antibody measurements in autoimmune thyroid disease and type 1 diabetes. J Immunol Methods. **154**: 61–68.
37 Horváth S, Mirnics K (2014). Immune system disturbances in schizophrenia [review]. Biol Psychiatry. **75**: 316–323.
38 Hwang Y, Kim J, Shin J-Y, Kim J-Il, Seo J-S, Webster MJ, et al. (2013). Gene expression profiling by mRNA sequencing reveals increased expression of immune/inflammation-related genes in the hippocampus of individuals with schizophrenia. Transl Psychiatry. **3**: e321.
39 Jeppesen R, Eriksen Benros M (2019). Autoimmune diseases and psychotic disorders [review]. Front Psychiatry. **10**: 131.
40 Jernbom Falk A, Galletly C, Just D, Toben C, Baune BT, Clark SR, et al. (2021). Autoantibody profiles associated with clinical features in psychotic disorders. Transl Psychiatry. **11**: 474.
41 Johansson V, Nybom R, Wetterberg L, Hultman CM, Cannon TD, Johansson AGM, et al. (2012). Microscopic particles in two fractions of fresh cerebrospinal fluid in twins with schizophrenia or bipolar disorder and in healthy controls. PLoS ONE. **7**: e45994.
42 Kagami M, Koike T, Maruyama N, Takabayashi K, Tomioka H, Yoshida S, et al. (1987). Cytotoxic anti-lymphocyte antibody in schizophrenics. J Neurol. **234**: 359–360.
43 Kapogiannis D, Dobrowolny H, Tran J, Mustapic M, Frodl T, Meyer-Lotz G, et al. (2019). Insulin-signaling abnormalities in drug-naïve first-episode schizophrenia: transduction protein analyses in extracellular vesicles of putative neuronal origin. Eur Psychiatry. **62**: 124–129.
44 Kay SR, Fiszbein A, Opler LA (1987). The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull. **13**: 261–276.
45 Kilidireas K, Latov N, Strauss DH, Gorig AD, Hashim GA, Gorman JM, et al. (1992). Antibodies to the human 60 kDa heat-shock protein in patients with schizophrenia. The Lancet. **340**: 569–572.
46 Kim SK, Park HJ, Kim YJ, Chung J-H, Yu GI, Kim YJ, et al. (2013). A polymorphism (rs4773092, Cys816Cys) of *IRS2* affects auditory hallucinations in schizophrenia patients [letter]. Psychiatry Res. **209**: 124–125.
47 Kim JJ, Lee SJ, Toh KY, Lee CU, Lee C, Paik IH (2001). Identification of antibodies to heat shock proteins 90 kDa and 70 kDa in patients with schizophrenia. Schizophr Res. **52**: 127–135.
48 Kirkpatrick B, Miller B, Garcia-Rizo C, Fernandez-Egea E (2014). Schizophrenia: a systemic disorder [review]. Clin Schizophr Relat Psychoses. **8**: 73–79.
49 Klyushnik TP, Danilovskaya EV, Vatolkina OE, Turkova IL, Tsutsul´kovskaya MYa, Orlova VA, et al. (1999). Changes in the serum levels of autoantibody to nerve growth factor in patients with schizophrenia. Neurosci Behav Physiol. **29**: 355–357.
50 Krischer JP, Lynch KF, Schatz DA, Ilonen J, Lernmark Å, Hagopian WA, et al. (2015). The 6 year incidence of diabetes-associated autoantibodies in genetically at-risk children: the TEDDY study. Diabetologia. **58**: 980–987.
51 Kullmann S, Heni M, Hallschmid M, Fritsche A, Preissi H, Häring H-U (2016). Brain insulin resistance at the crossroads of metabolic and cognitive disorders in humans [review]. Physiol Rev. **96**: 1169–1209.
52 Laskaris LE, Di Biase MA, Everall I, Chana G, Christopoulos A, Skafidas E, et al. (2016). Microglial activation and progressive brain changes in schizophrenia [review]. Br J Pharmacol. **173**: 666–680.
53 Lennox BR, Palmer-Cooper EC, Pollak T, Hainsworth J, Marks J, Jacobson L, et al. (2017). Prevalence and clinical characteristics of serum neuronal cell surface antibodies in first-episode psychosis: a case-control study. Lancet Psychiatry. **4**: 42–48.
54 Leypoldt F, Armangue T, Dalmau J (2015). Autoimmune encephalopathies [review]. Ann N Y Acad Sci. **1338**: 94–114.
55 Liao P, Soong TW (2010). Cav1.2 channelopathies: from arrhythmias to autism, bipolar disorder, and immunodeficiency. Eur J Physiol. **460**: 353–359.
56 Mané-Damas M, Hoffmann C, Zong S, Tan A, Molenaar PC, Losen M, et al. (2019). Autoimmunity in psychotic disorders. Where we stand, challenges and opportunities. Autoimmun Rev. **18**: 102348.
57 McClenaghan NH, Flatt PR (1999). Physiological and pharmacological regulation of insulin release: insights offered through exploitation of insulin-secreting cell lines [review]. Diabetes Obes Metab. **1**: 137–150.
58 McGrath J, Saha S, Chant D, Welham J (2008). Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev. **30**: 67–76.
59 Melkersson K (2009). Familial and sporadic schizophrenia: a comparison of somatic diseases and abuse in patients and their relatives. Acta Neuropsychiatr. **21**: 4–10.
60 Melkersson K (2010). Clinical findings related to alterations of the intracellular calcium homeostasis in schizophrenia [review]. Prog Neuropsychopharmacol Biol Psychiatry. **34**: 1365–1366.
61 Melkersson K (2013). Case report of a patient with schizophrenia and a mutation in the insulin receptor substrate-4 gene. Neuroendocrinol Lett. **34**(3): 173–176.
62 Melkersson K, Bensing S (2018). Signs of impaired blood-brain barrier function and lower IgG synthesis within the central nervous system in patients with schizophrenia or related psychosis, compared to that in controls. Neuroendocrinol Lett. **39**(1): 33–42.
63 Melkersson K, Bensing S (2021). Increased antibody reactivity against insulin receptor-A and insulin like growth factor 1 receptor and their ligands in cerebrospinal fluid and serum of patients with schizophrenia or related psychosis. Neuroendocrinol Lett. **42**(5): 339–358.
64 Melkersson K, Persson B (2011). Association between body mass index and insulin receptor substrate-4 (*IRS-4*) gene polymorphisms in patients with schizophrenia. Neuroendocrinol Lett. **32**(5): 634–640.
65 Melkersson K, Persson B (2012). Evidence for a negative association between schizophrenia and a polymorphism in the insulin receptor substrate-3 (*IRS-3*) gene. Neuroendocrinol Lett. **33**(3): 321–330.
66 Melkersson K, Persson B, Hongslo T (2011). The insulin receptor substrate-4 (*IRS-4*) gene and schizophrenia: no evidence for a main genetic factor, however one report of a single schizophrenia patient with a mutation. Neuroendocrinol Lett. **32**(1): 51–58.
67 Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B (2011). Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry. **70**: 663–671.
68 Mobarrez F, Nybom R, Johansson V, Hultman CM, Wallén H, Landén M, et al. (2013). Microparticles and microscopic structures in three fractions of fresh cerebrospinal fluid in schizophrenia: case report of twins. Schizophr Res. **143**: 192–197.
69 Moises HW, Zoega T, Gottesman II (2002). The glial growth factors deficiency and synaptic destabilization hypothesis of schizophrenia. BMC Psychiatry. **2**: 8.
70 Molholm HB (1942). Hyposensitivity to foreign protein in schizophrenic patients. Psychiatr Quarterly. **16**: 565–571.
71 Moller DE, Yokota A, Caro JF, Flier JS (1989). Tissue-specific expression of two alternatively spliced insulin receptor mRNAs in man. Mol Endocrinol. **3**: 1263–1269.
72 Momtazmanesh S, Zare-Shahabadi A, Rezaei N (2019). Cytokine alterations in schizophrenia: an updated review. Front Psychiatry. **10**: 892.
73 Mongan D, Ramesar M, Föking M, Cannon M, Cotter D (2020). Role of inflammation in the pathogenesis of schizophrenia: A review of the evidence, proposed mechanisms and implications for treatment. Early Intervention in Psychiatry. **14**: 385–397.
74 Mosthaf L, Grako K, Dull TJ, Coussens L, Ullrich A, McClain DA (1990). Functionally distinct insulin receptors generated by tissue-specific alternative splicing. EMBO J. **9**: 2409–2413.
75 Müller N, Ackenheil M, Hofschuster E, Mempel W, Eckstein R (1991). Cellular immunity in schizophrenic patients before and during neuroleptic treatment. Psychiatry Res. **37**: 147–160.
76 Müller N, Riedel M, Ackenheil M, Schwarz MJ (2000). Cellular and humoral immune system in schizophrenia: a conceptual reevaluation [review]. World J Biol Psychiatry. **1**: 173–179.
77 Najjar S, Pearlman D, Zagzag D, Golfinos J, Devinsky O (2012). Glutamic acid decarboxylase autoantibody syndrome presenting as schizophrenia. The Neurologist. **18**: 88–91.

78 Oviedo-Salcedo T, de Witte L, Kümpfel T, Kahn RS, Falkai P, Eichhorn P, et al. (2018). Absence of cerebrospinal fluid anti-neuronal antibodies in schizophrenia spectrum disorders. Br J Psychiatry. **212**: 318–320.
79 Palmer JP, Asplin CM, Clemons P, Lyen K, Tatpati O, Raghu PK, et al. (1983). Insulin antibodies in insulin-dependent diabetics before insulin treatment. Science. **222**: 1337–1339.
80 Pardiñas AF, Holmans P, Pocklington AJ, Escott-Price V, Ripke S, Carrera N, et al. (2018). Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. Nat Genet. **50**: 381–389.
81 Ponsford M, Castle D, Tahir T, Robinson R, Wade W, Steven R, et al. (2019). Clozapine is associated with secondary antibody deficiency. Br J Psychiatry. **214**: 83–89.
82 Popova NN (1977). Investigation of brain autoantigens in the blood serum of schizophrenics. Neurosci Behav Physiol. **8**: 76–81.
83 Pozzilli P, Manfrini S, Monetini L (2001). Biochemical markers of type 1 diabetes: clinical use. Scand J Clin Lab Invest. **61**(suppl 235): 38–44.
84 Ripke S, Neale BM, Corvin A, Walters JT, Farh K-H, Holmans PA, et al. (2014). Biological insights from 108 schizophrenia-associated genetic loci. Nature. **511**: 421–427.
85 Rubin RP (1970). The role of calcium in the release of neurotransmitter substances and hormones [review]. Pharmacol Rev. **22**: 389–428.
86 Sara VR, Hall K, von Holtz H, Humbel R, Sjögren B, Wetterberg L (1982). Evidence for the presence of specific receptors for insulin-like growth factors 1 (IGF-1) and 2 (IGF-2) and insulin throughout the adult human brain. Neurosci Lett. **34**: 39–44.
87 Schizophrenia Working Group of the Psychiatric Genomics Consortium (2022). Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature. **604**: 502–508.
88 Schlaaff K, Dobrowolny H, Frodl T, Mawrin C, Gos T, Steiner J, et al. (2020). Increased densities of T and B lymphocytes indicate neuroinflammation in subgroups of schizophrenia and mood disorder patients. Brain Behav Immun. **88**: 497–506.
89 Schlosser M, Mueller PW, Achenbach P, Lampasona V, Bingley PJ (2011). Diabetes antibody standardization program. First evaluation of assays for autoantibodies to IA-2ß. Diabetes Care. **34**: 2410–2412.
90 Schmitt A, Leonardi-Essmann F, Durrenberger PF, Parlapani E, Schneider-Axmann T, Spanagel R, et al. (2011). Regulation of immune-modulatory genes in left superior temporal cortex of schizophrenia patients: a genome-wide microarray study. World J Biol Psychiatry. **12**: 201–215.
91 Schulingkamp RJ, Pagano TC, Hung D, Raffa RB (2000). Insulin receptors and insulin action in the brain: review and clinical implications. Neurosci Biobehav Rev. **24**: 855–872.
92 Schwarz MJ, Riedel M, Ackenheil M, Müller N (2000). Decreased levels of soluble intercellular adhesion molecule-1 (sICAM-1) in unmedicated and medicated schizophrenic patients. Biol Psychiatry. **47**: 29–33.
93 Schwarz MJ, Riedel M, Gruber R, Ackenheil M, Müller N (1999). Antibodies to heat shock proteins in schizophrenic patients: implications for the mechanism of the disease. Am J Psychiatry. **156**: 1103–1104.
94 Schwarz MJ, Riedel M, Gruber R, Müller N, Ackenheil M (1998). Autoantibodies against 60-kDa heat shock protein in schizophrenia. Eur Arch Psychiatry Clin Neurosci. **248**: 282–288.
95 Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, et al. (2016). Schizophrenia risk from complex variation of complement component 4. Nature. **530**: 177–183.
96 Sesti G, Tullio AN, D'Alfonso R, Napolitano ML, Marini MA, Borboni P, et al. (1994). Tissue-specific expression of two alternatively spliced isoforms of the human insulin receptor protein. Acta Diabetol. **31**: 59–65.
97 Shcherbakova IV, Siryachenko TM, Mazaeva NA, Kaleda VG, Krasnolobova SA, Klyushnik TP (2004). Leukocyte elastase and autoantibodies to nerve growth factor in the acute phase of schizophrenia and their relationship to symptomatology. World J Biol Psychiatry. **5**: 143–148.
98 Shinitzky M, Deckmann M, Kessler A, Sirota P, Rabbs A, Elizur A (1991). Platelet autoantibodies in dementia and schizophrenia – possible implication for mental disorders. Ann N Y Acad Sci. **621**: 205–217.
99 Spivak B, Schechtman M, Blumensohn R, Schönherz-Pine Y, Yoran-Hegesh R, Deckmann M, et al. (2009a). Blind verification of elevated platelet autoantibodies in serum of schizophrenic patients – part I: young subjects. Neuropsychobiology. **60**: 44–48.
100 Spivak B, Schechtman M, Schönherz-Pine Y, Blumensohn R, Mostovoy S, Amital D, et al. (2009b). Blind verification of elevated platelet autoantibodies in serum of schizophrenic patients – part II: adult subjects. Neuropsychobiology. **60**: 49–54.
101 Steiner J, Jacobs R, Panteli B, Brauner M, Schiltz K, Bahn S, et al. (2010). Acute schizophrenia is accompanied by reduced T cell and increased B cell immunity. Eur Arch Psychiatry Clin Neurosci. **260**: 509–518.
102 Steiner J, Walter M, Glanz W, Sarnyai Z, Bernstein H-G, Vielhaber S, et al. (2013). Increased prevalence of diverse *N*-methyl-D-aspartate glutamate receptor antibodies in patients with an initial diagnosis of schizophrenia. JAMA Psychiatry. **70**: 271–278.
103 Theorell J, Ramberger M, Harrison R, Mgbachi V, Jacobson L, Waters P, et al. (2021). Screening for pathogenic neuronal autoantibodies in serum and CSF of patients with first-episode psychosis. Transl Psychiatry. **11**: 566.
104 Tong J, Huang J, Luo X, Chen S, Cui Y, An H, et al. (2019). Elevated serum anti-NMDA receptor antibody levels in first-episode patients with schizophrenia. Brain Behav Immun. **81**: 213–219.
105 Trépanier MO, Hopperton KE, Mizrahi R, Mechawar N, Bazinet RP (2016). Postmortem evidence of cerebral inflammation in schizophrenia: a systematic review. Mol Psychiatry. **21**: 1009–1026.
106 Uchigata Y, Eguchi Y, Takayama-Hasumi S, Omori Y (1994). Insulin autoimmune syndrome (Hirata Disease): clinical features and epidemiology in Japan. Diabetes Res Clin Pract. **22**: 89–94.
107 Upthegrove R, Manzanares-Teson N, Barnes NM (2014). Cytokine function in medication-naïve first episode psychosis: a systematic review and meta-analysis. Schizophr Res. **155**: 101–108.
108 van Beveren NJM, Schwarz E, Noll R, Guest PC, Meijer C, de Haan L, et al. (2014). Evidence for disturbed insulin and growth hormone signaling as potential risk factors in the development of schizophrenia. Transl Psychiatry. **4**: e430.
109 van Mierlo HC, Broen JCA, Kahn RS, de Witte LD (2019). B-cells and schizophrenia: A promising link or a finding lost in translation? [review]. Brain Behav Immun. **81**: 52–62.
110 Vitaliani R, Mason W, Ances B, Zwerdling T, Jiang Z, Dalmau J (2005). Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. Ann Neurol. **58**: 594–604.
111 Von Knorring L, Lindström E (1992). The Swedish version of the Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Construct validity and interrater reliability. Acta Psychiatr Scand. **86**: 463–468.
112 Wang L-Y, Chen S-F, Chiang J-H, Hsu C-Y, Shen Y-C (2018). Autoimmune diseases are associated with an increased risk of schizophrenia: a nationwide population-based cohort study. Schizophr Res. **202**: 297–302.
113 Wang X-F, Wang D, Zhu W, Delrahim KK, Dolnak D, Hyman Rapaport M (2003). Studies characterizing 60 kDa autoantibodies in subjects with schizophrenia. Biol Psychiatry. **53**: 361–375.
114 Weissleder C, Webster MJ, Barry G, Shannon Weickert C (2021). Reduced insulin-like growth factor family member expression predicts neurogenesis marker expression in the subependymal zone in schizophrenia and bipolar disorder. Schizophr Bull. **47**: 1168–1178.
115 Wetterberg L, Nybom R, Bratlid T, Fladby T, Olsson B, Wigzell H (2002). Micrometer-sized particles in cerebrospinal fluid (CSF) in patients with schizophrenia. Neurosci Lett. **329**: 91–95.
116 Wilkin TJ (1991). Autoantibodies as mechanisms, markers, and mediators of ß-cell disease [review]. Diabetes Metab Rev. **7**: 105–120.
117 Wozniak M, Rydzewski B, Baker SP, Raizada MK (1993). The cellular and physiological actions of insulin in the central nervous system [review]. Neurochem Int. **22**: 1–10.

118 Wu X, Huang Z, Wu R, Zhong Z, Wei Q, Wang H, et al. (2013). The comparison of glycometabolism parameters and lipid profiles between drug-naïve, first-episode schizophrenia patients and healthy controls. Schizophr Res. **150**: 157–162.
119 Yang Y-J, Luo T, Zhao Y, Jiang S-Z, Xiong J-W, Zhan J-Q, et al. (2020). Altered insulin-like growth factor-2 signaling is associated with psychopathology and cognitive deficits in patients with schizophrenia. PloS ONE. **15**: e0226688.
120 Zandi MS, Irani SR, Lang B, Waters P, Jones PB, McKenna P, et al. (2011). Disease-relevant autoantibodies in first episode schizophrenia. J Neurol. **258**: 686–688.
121 Zhao Z, Ksiezak-Reding H, Riggio S, Haroutunian V, Pasinetti GM (2006). Insulin receptor deficits in schizophrenia and in cellular and animal models of insulin receptor dysfunction. Schizophr Res. **84**: 1–14.
122 Özek M, Töreci K, Akkök I, Güvener Z (1971). The influence of treatment with neuroleptics upon the antibody-formation. Psychopharmacologia. **21**: 401–412.