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State marker properties of niacin skin sensitivity in ultra-high risk groups for psychosis - An optical reflection spectroscopy study☆

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ABSTRACT

Impaired niacin sensitivity (NS) is one of the most replicated findings in untreated schizophrenia, and reflects a disturbance of prostaglandin-mediated pathways in association with deregulated arachidonic acid metabolism, pro-inflammatory activation, and vasomotor function. In ultra-high risk individuals (UHR) increased NS was reported recently, pointing towards dynamic alterations of the underlying pathomechanisms in the period preceding psychosis. However, these characteristics are still unresolved in the diverse UHR groups.

We tested the hypothesis that NS is attenuated in patients who have transitioned to psychosis and in the Brief Limited Intermittent Psychotic Symptoms (BLIPS, UHR-B) and/or the attenuated symptoms (UHR-A) groups, while it is unchanged or increased in the genetic risk group (UHR-G).

Sensitivity to three concentrations (0.1–0.001 M) of aqueous methylnicotinate was tested in 84 UHR patients, 105 first-episode psychosis patients (FEP) and 180 healthy individuals (HC), using optical reflection spectroscopy (ORS).

The UHR subgroup and transition/non-transition outcomes were assessed according to PACE criteria using the CAARMS. Psychopathology was assessed using SANS, SAPS, and BPRS or SCL-90-R self-ratings.

In 0.001 M data, decreased NS was found in the UHR-B (n = 12), UHR-A (n = 45) and the transition groups (n = 13), similar to the result in FEP. NS in the UHR-G (n = 27) and HC groups did not differ. In the UHR-B and FEP groups, NS and positive symptom scores were inversely correlated.

These state marker properties could be used to characterize the intensity of the underlying pathomechanisms during the onset of psychosis or to identify UHR individuals that might benefit from related indicated prevention strategies.

1. Introduction

Impaired flush response to niacin (vitamin B_3) stimulation (niacin sensitivity, NS) was first reported in schizophrenia by Hoffer (Hoffer and Osmond, 1962), and can be assessed by standardized semi-quantitative visual rating scales (Kerr et al., 2008; Ward et al., 1998) and several objective measurement techniques, including laser Doppler flowmetry (Messamore et al., 2010; Yao et al., 2016), photoplethysmography (Wilson and Douglass, 1986) or malar temperature (Fiedler et al., 1986). A combined method study was performed by Rybakowski and Weterle using an oral challenge dose of 200 mg niacin and two different techniques (thermometric recordings and visual ratings) (Rybakowski and Weterle, 1991).

Attenuated NS is one of the well-replicated biological findings in schizophrenia (Messamore, 2003; Nadalin et al., 2010; Smesny et al., 2003; Smesny et al., 2005; Yao et al., 2016). Following the discovery of the underlying pathomechanisms, impairment of NS has been integrated in the prostaglandin deficiency hypothesis (Horrobin, 1977), and later the membrane lipid hypothesis (Horrobin, 1998; Horrobin et al., 1994) of schizophrenia. The prostaglandin-mediated pathway involves G protein-coupled nicotinic acid receptor stimulation at epidermal Langerhans cells, Ca^{2+} dependent expression of prostaglandin synthases, and the formation of vasodilatory prostaglandins (PGD_2) (Benyo et al., 2006; Maciejewski-Lenoir et al., 2006; Offermanns, 2006). In animals, dietary polyunsaturated fatty acid (PUFA) deprivation is associated with altered expression of the enzymes in the arachidonic acid (20:4n-6, ARA) cascade (cytosolic phospholipase A2 - cPLA2,

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respectively) and the docosahexaenoic acid (22:6n-3, DHA) cascade (calcium-independent phospholipase A2 - iPLA2, respectively) (Rao et al., 2007). Furthermore, administration of acetylsalicylic acid reduced skin flushing by 30% (Papaliodis et al., 2008). Similarly, in humans attenuated NS has been directly correlated with decreased PUFA precursors of prostaglandins (Berger et al., 2016; Glen et al., 1996) and is almost completely abolished by acetylsalicylic acid (Smesny et al., 2003). Additional findings in first-episode schizophrenia patients (FEP) further support the association of NS with pro-inflammatory activation (Milleit et al., 2010), while studies in medicated patients relate NS to vasomotor function (Messamore et al., 2010). Taken together, this evidence supports the notion of NS as a marker of deprivation of PUFA, and possibly also of a non-specific pro-inflammatory activation, alterations that are specified within both the membrane lipids (Horrobin et al., 1994) and neuroinflammatory concepts of schizophrenia (Bechter, 2013; Fillman et al., 2015; Goldsmith et al., 2016; Upthegrove et al., 2014).

In research on psychosis prevention and early intervention, the investigation of biological markers, such as NS, has increasingly gained attention in order to define risk groups according to biological (instead of psychometric) criteria (Fusar-Poli et al., 2016a; Fusar-Poli et al., 2016b) to enable the prediction of transition/non-transition, functional outcomes (Emanuele et al., 2012; Gifford et al., 2016) and treatment response (Rapaport et al., 2016). So far, the available research on NS in this field has revealed inconclusive results. In the entire group of ultra-high risk (UHR) individuals the most recent study has shown increased (instead of decreased) NS (Berger et al., 2016), while previous smaller studies in genetic risk groups revealed attenuated (Lin et al., 2007; Shah et al., 1999; Waldo, 1999) or unchanged (Nikolov et al., 2002; Smesny et al., 2007a) skin responses. These findings suggest dynamic changes of NS around the time of the first acute psychotic episode (Smesny et al., 2005). However, having not stratified their UHR individuals according to the PACE (Personal Assessment and Crisis Evaluation) subgroups (Yung et al., 2012; Yung et al., 2008) and psychopathology, Berger and colleagues were not able to further explore their unexpected finding (Berger et al., 2016).

By investigating a completely different (i.e. non-overlapping) population, and using an objective assessment technique of skin flush response (optical reflection spectroscopy, ORS), the present study aimed to further resolve the state marker properties of NS; namely, differential response in UHR subgroups (according to PACE criteria), associations with symptomatology, and predictive validity in terms of transition outcome. Therefore, our hypotheses are:

I) that alterations of NS vary across the different UHR subgroups according to PACE criteria (BLIPS group, UHR-B; attenuated symptoms group, UHR-A; genetic risk group, UHR-G).
II) that NS differs between transition (UHR-T) and non-transition (UHR-NT) individuals, where transition individuals show similar NS alterations as FEP, and
III) that NS in UHR individuals is associated with psychopathology, as previously shown in schizophrenia patients by our (Smesny et al., 2007b) and other (Glen et al., 1996) groups.

2. Methods

2.1. Description of study population

Niacin skin tests were performed on 84 UHR individuals (54 male, 30 female; detailed demographic information is provided in Table 1), 105 FEP (69 male, 36 female), and 180 healthy controls (HC; 88 male, 92 female). The group of UHR individuals included 45 assigned to the UHR-A group (30 male, 15 female), 12 assigned to the UHR-B group (11 male, 1 female) and 27 assigned to the UHR-G group (13 male, 14 female). One individual belonged to the UHR-A as well as the UHR-G subgroup, and was assigned to the UHR-A subgroup. UHR subjects and patients were recruited at the Department of Child and Adolescent Psychiatry and Department of Psychiatry and Psychotherapy of Jena University Hospital. All controls were recruited by newspaper advertisements and were paid for their participation. The recruitment period was three years.

Table 1
Demographic details and psychopathology scores of participants (healthy controls, HC; first-episode patients, FEP; UHR with attenuated symptoms, UHR-A; UHR with BLIPS, UHR-B; UHR with genetical risk, UHR-G).

	HC	FEP	UHR-A	UHR-B	UHR-G
n	180	105	45	12	27
m (%)	88 (48.89%)	69 (65.71%)	30 (66.67%)	11 (91.67%)	13 (48.15%)
Age (SD)	26.12 (8.13)	22.45 (5.85)	22.78 (4.16)	20.75 (4.99)	16.85 (3.58)
Nicotine					
Yes/no	48/131	69/32	26/18	11/1	11/15
No information	1	4	1	0	1
Cannabis					
Yes/no	0/179	36/68	12/31	9/3	5/21
No information	1	1	2	0	1
Alcohol					
No	19	11	6	1	
One or two times/year	7	5	5	0	1
Monthly	16	10	6	2	
Weekly	18	6	8	2	
Daily	3	6	5	0	
No information	117	67	15	7	26
Antipsychotic medication					
None		39	45	12	
Quetiapine		31	0	0	
Aripiprazole		7	0	0	
Risperidone		27	0	0	
Amisulpride		1	0	0	
Psychopathology					
SANS total (SD)		43.11 (25.13)	42.25 (26.54)	32.40 (18.24)	
SAPS total (SD)		41.57 (22.92)	30.20 (16.40)	39.33 (22.89)	
BPRS total (SD)		47.06 (16.21)	46.85 (13.84)	40.45 (11.43)	
SCL-90-R GSI (SD)	0.15 (0.19)	0.96 (0.77)	1.11 (0.58)	0.38 (0.20)	0.51 (0.41)

UHR individuals had not received treatment with antipsychotic agents. About one-third of them took selective serotonin re-uptake inhibitors (SSRI, in most cases citalopram at a maximum dose of 20 mg/d). In the FEP group, 39 participants were neuroleptic-naïve. If FEP were treated, they took second-generation antipsychotics at low-to-moderate dose (quetiapine 50–100 mg/d, aripiprazole 5–15 mg/d, amisulpride 200–400 mg/d, risperidone 1–3 mg/d). All HC were free of any medication at the time of measurement. Detailed information on medication, as well as use of nicotine, alcohol or cannabis is given in Table 1.

The study was approved by the Research Ethics Committee of the University Hospital Jena. All subjects (and their parents if subjects were younger than 18 years) gave written informed consent to participate in this study.

2.2. Psychiatric measures

For UHR assessments CAARMS (Comprehensive Assessment of At Risk Mental States) interviews (Yung et al., 2002) were performed. Psychopathology ratings in FEP were performed using the scales for the assessment of positive/negative symptoms (SAPS (Andreasen, 1984), SANS (Andreasen, 1981)) and the brief psychiatric rating scale (BPRS (Overall and Gorham, 1962)). CAARMS interviews in UHR patients and clinical assessments in FEP including making of diagnoses were

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