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NIACIN SKIN FLUSH TEST: A RESEARCH TOOL FOR STUDYING SCHIZOPHRENIA

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SUMMARY

Background: *A body of biochemical evidence suggests that abnormal phospholipid metabolism may play a role in the etiology of schizophrenia, and possibly, other psychiatric and neurological diseases. Niacin, a B-complex vitamin, induces prostaglandin synthesis, vasodilatation, and skin flushing when applied as a solution on the skin or taken orally. In schizophrenia, diminished or absent skin response to niacin represents a robust finding.*

Results: *Attenuated niacin skin-flush response has been analysed as a potential biochemical marker of impaired prostaglandin signaling in schizophrenia. Diminished skin redness after topical application of niacin might be caused by a reduced level of the precursor arachidonic acid in the peripheral membranes, increased activity of the enzyme phospholipase A2, abnormal expression of niacin or prostaglandin receptors, or poor vasomotor activity of cutaneous capillary walls. Heritability estimates established in several studies support niacin skin flush response as a vulnerability trait for the development of psychosis. However, the exact mechanism of a reduced skin flush, the possible influence of the long-term use of antipsychotics, and the usefulness of the test for diagnostic purpose are not clear yet.*

Conclusions: *Niacin skin flush test is a simple, non-invasive and easily replicable method in the research of schizophrenia. The studies investigating niacin flushing in schizophrenia are numerous but incoherent regarding methods of niacin application and evaluation of the results. New studies, controlling adequately for age, sex, drug abuse, diet, as well as genetic factors that may influence the intensity and reaction time, are necessary to clarify the usefulness of niacin testing in psychiatry.*

Key words: *niacin skin-flush test – schizophrenia - metabolic cascade of arachidonic acid - polyunsaturated fatty acids - cell signaling*

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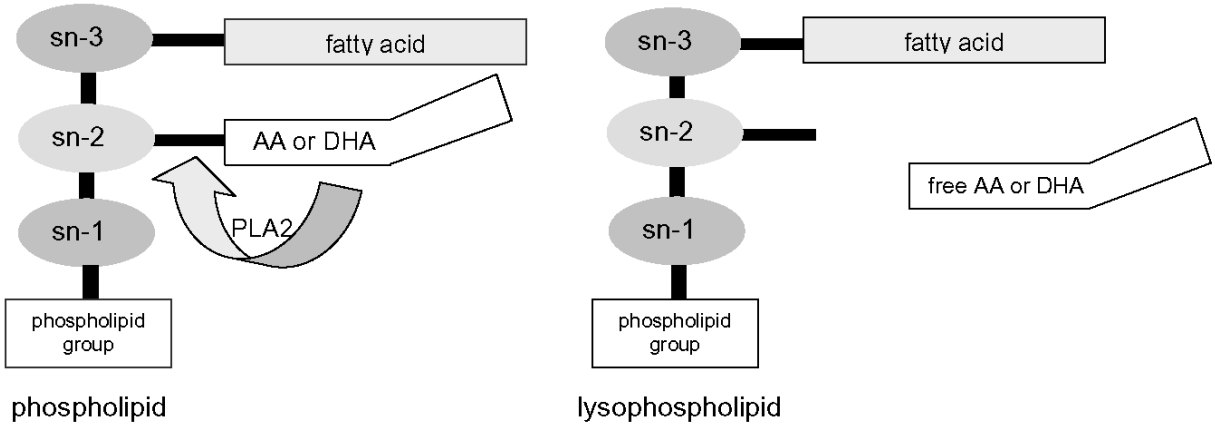
INTRODUCTION

Schizophrenia is a neurodevelopmental and neurodegenerative disease characterized by the disturbance of multiple neurotransmitter signaling pathways. Since long chain polyunsaturated fatty acids (LC-PUFAs) are essential for normal development, structure and function of the brain, it is highly probable that a disturbance of their metabolism participates in the etiology of schizophrenia, depression and other mental diseases. The human body has lost the ability of *de novo* synthesis of LC-PUFAs, therefore, they have to be present in the diet. Linoleic acid (LA, 18:2n-6) and alpha-linolenic acid (ALA, 18:3n-3) are essential fatty acids (EFAs) composed of 18 carbon atoms. Symbols n-3 and n-6 are synonyms for the terms ω-3 and ω-6 that indicate the location of the last double covalent bond in the fatty acid molecule, beginning at the end of the carbon chain. The EFAs are a substrate for fatty acid desaturases and elongases that can metabolize them into forms with more unsaturated bonds and longer chains. These forms may be incorporated into membrane phospholipids. The release of arachidonic acid (AA, 20:4n-6), docosahexaenic acid (DHA, 22:6n-

3) and other fatty acids from the membrane phospholipid molecules (which are structural components of biological membranes) constitutes a part of neuronal impulse transmission. The released fatty acids, particularly AA, and their derivates (prostaglandins, leukotrienes, thromboxanes) are important signaling molecules, but these substances are also recognized mediators of inflammation. Neuronal membranes are rich in DHA (~50%) (Singh 2005), particularly in the cytosolic portion of the phospholipid double layer, indicating an important role of this fatty acid in the structure and function of neurons. The role of DHA has been recognized during pre-natal development. In the rat brain, the accumulation of DHA followed the period of active neurogenesis and synaptogenesis (Yavin 2006). The DHA/AA (n-3/n-6) ratio is important in the maintenance of an appropriate level of biological membrane fluidity, which is essential for ion channels function, membrane receptor activity, release of neurohormones, i.e. the signaling processes of every cell. Disruption of multiple neurotransmitters in schizophrenia (dopamine, serotonin, norepinephrine, epinephrine, glutamate, GABA-ergic) supports the phospholipid hypothesis that places neuronal membranes and membrane – related processes in the center of the pathophysiology of this disease (Skosnik & Yao 2003, du Bois et al. 2005).

Fatty acids in the membranes are bound to the trivalent alcohol glycerol within the phospholipid molecules; during neuronal transmission they are released by the phospholipase (PLA) group of enzymes. AA and DHA are incorporated in the phospholipid molecules mostly at the position sn-2 (Figure 1); in their release from the membrane the phospholipase A2 family (PLA2) is engaged. Cytosolic, calcium – dependent phospholipase A2 (cPLA2, product of PLA2G4A gene, 1q25) catalyses mostly the release of AA, while calcium – independent phospholipase A2 (iPLA2, product of PLA2G6A gene, 22q13.1) participates in the release of DHA (Green et al. 2008). After releasing the fatty acid from the sn-2 position, the remaining lysophospholipid may act as an important signaling molecule as well as a mediator for phagocyte infiltration in the inflammatory response (Zhang et al. 2007).



Legend: AA-arachidonic acid; DHA– docosahexaenoic acid; PLA2-phospholipase A2;

Figure 1. Deacylation of arachidonic or docosahexaenoic acid by phospholipase A2

Enzymes of the PLA2 family work in the areas of neuronal membranes that contain monoamine receptors and are directly linked to neurotransmission. Numerous studies have indicated that a deficit of AA and n-3 group fatty acids in the membranes of peripheral and central cells of schizophrenic patients may be casually related to an increased activity of PLA2 enzymes (Gattaz et al. 1987, Ross et al. 1997, Barbosa et al. 2007), although dietary factors (Calder 2006, Peet 2006, Rapoport 2008), effect of medications (Chen et al. 2008), oxidative stress (Mahadik et al. 2001), and desaturase abnormalities (Nakada et al. 1990, Williard et al. 2001) have also been suggested as causative factors of FA deficiencies. As a consequence of an increased PLA2 activity there would follow an increased release of LC-PUFAs from membrane phospholipids, increased synthesis of pro-inflammatory mediators (AA derivates), augmented peroxidation of lipids and free radicals formation; finally resulting in an imbalance of membrane phospholipid fatty acids turnover.

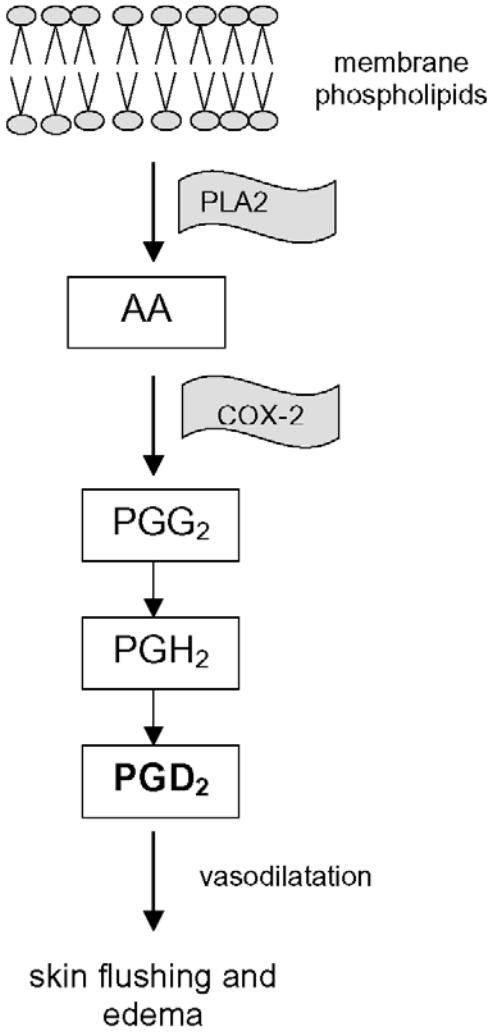
Different studies have suggested a disturbance of metabolic cascade that starts with PLA2 activity in patients suffering from schizophrenia, bipolar disorder and depression, and re-establishment of the equilibrium following continuous long-term (but not acute) antipsychotic drug treatment (McNamara et al. 2006).

No highly specific biochemical tests that could contribute to the diagnosis of mental illnesses have been developed so far. However, a series of studies have shown attenuated response (no flushing) after oral or cutaneous application of niacin in 24 – 90% of patients with schizophrenia. This phenomenon has been the core of the hypothesis about the phospholipid disorder in schizophrenia (Messamore 2003). The aim of this paper is to provide an overview of published data regarding the application and results of niacin testing in patients suffering from schizophrenia and other mental illnesses in order to evaluate its potential diagnostic value.

MECHANISM OF NIACIN ACTION

Niacin, also known as nicotinic acid, is a water-soluble B complex vitamin. Being a precursor of nicotinamide adenine dinucleotides (NADH, NAD, NAD^+) and nicotinamide adenine dinucleotide phosphate (NADP), niacin has an important role in many metabolic pathways. Niacin derivates participate in detoxication processes, DNA repair, and synthesis of steroid hormones in the suprarenal gland. The human liver can synthesize niacin from the essential amino acid tryptophan; it takes 60 mg of tryptophan to synthesize 1 mg of niacin (Jacobson 2007). Gross alimentary deficit of niacin can cause pellagra, while a moderate deficit decreases the intensity of metabolism and causes a decreased sensitivity to coldness. Possible side effects of therapeutic doses of niacin are dry mouth and skin rash, gastrointestinal disturbance, arrhythmia, hyperglycemia, hyperuricaemia, while high doses can cause macular and retinal alterations. However, the most frequently observed side effect of niacin is skin flushing following oral or cutaneous application of niacin (Murrell & Taylor 1959).

Niacin exhibits its action by binding to appropriate receptors in skin macrophages and epidermal Langerhans cells (Bosveld-van Haandel et al. 2006, Smesny et al. 2007). That is followed by the synthesis and release of prostaglandins D2 and E2 (PGD_2 and PGE_2) (Figure 2). Serum concentration of prostaglandins following niacin priming can be increased up to several hundred times (Hudson et al. 1997, Nilsson et al. 2006).



Legend: PLA2-phospholipase A2; AA-arachidonic acid; COX-2 – cyclooxygenase-2; PGG_2-prostaglandin G_2; PGH_2-prostaglandin H_2; PGD_2-prostaglandin D_2

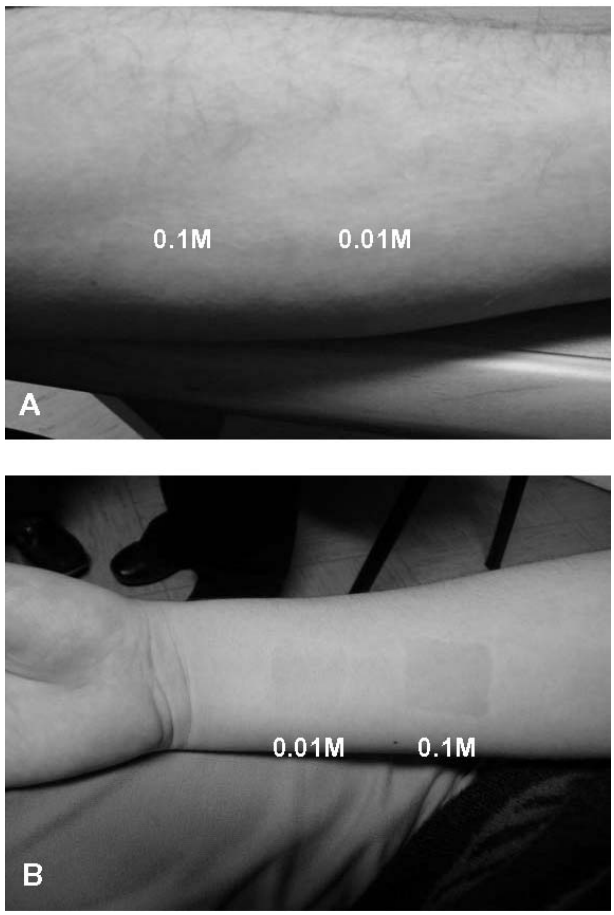
Figure 2. The part of the metabolic cascade of arachidonic acid

The precursor molecule, pivotal for prostaglandin synthesis, is AA (Ward et al. 1998, Nilsson et al. 2006). AA is released from membrane phospholipids by the action of PLA2 enzyme and is further metabolized into prostaglandin molecules by the action of cyclooxygenase-2 (COX-2) (Tavares et al. 2003, Nilsson et al. 2006). Prostaglandins stimulate the production of cyclic AMP, which causes relaxation of smooth muscles in skin capillary walls, and consequent vasodilatation (Hudson et al. 1999

Messamore 2003), flushing and edema. Therefore, abnormalities within the PLA2/COX2 cascade pathway may affect the flush response to niacin (Maclean et al. 2003). Niacin non-responsiveness may, among other possibilities, indicate the disturbance of the membrane phospholipid metabolism that results in a decreased concentration of AA, which is an indispensable precursor of prostaglandins (Glen et al. 1996, Smesny et al. 2007).

METHODS OF NIACIN APPLICATION AND EVALUATION OF SKIN RESPONSE

Murrell & Taylor (1959) discovered the body's response to niacin. While attempting to treat patients with schizophrenia with high oral doses of niacin (up to 3 g daily), Hoffer (1962) noticed an unusually high tolerance against its skin flush effects. Altered skin response to niacin in patients with schizophrenia was also noticed following oral application of lower doses of niacin (from 25 mg to 250 mg) (Fiedler et al. 1986, Horrobin 1980). Ward et al. (1998) introduced the local application of methyl-nicotinate (skin-permeable ester of nicotinic acid) via a plastic strip with four pockets containing absorbent paper that was attached to the volar side of the lower arm. This method of application greatly reduced the systemic adverse effects of oral application as well as suspiciousness and discomfort of the patients. It further reduced the duration of the test and enabled a more objective evaluation of the test results (Figure 3). An advantage of the local application of niacin is the possibility of simultaneous application of solutions of different concentrations (0.1 M; 0.01 M; 0.001M; 0.0001M). It offers a possibility to determine the optimal concentration for differentiation between tested subjects and controls. The effect of oral niacin test was evaluated by visual inspection of facial and upper body skin flushing (Horrobin 1980), by skin temperature measurement (Fiedler et al. 1986), by measurement of temperature change in the ear lobe (Rybakovski & Weterle 1991), or by photoplethysmography (a method of determination in which the intensity of light reflected from the skin surface and the red cells below is measured to determine the blood volume of the respective area) (Wilson & Douglass 1986), while Hudson et al. (1997) introduced the thermal index, i.e.the ratio of skin vs. body temperature. The increase of skin temperature of



Legend: A) weak (0.1M) and negative (0.01M) skin response
B) positive skin responses

Figure 3. Niacin skin flush response (after applying 0.01M and 0.1M niacin solution for 5 min)

1.5 to 2ºC at the outer rim of the ear (pinna) was considered to be a positive niacin response. After the introduction of local application of niacin, the scales that define the intensity of the response were applied for skin redness evaluation. Ward et al. (1998) proposed the score 0 to 3 (0=no erythema, 1=incomplete erythema, 2=complete erythema with the definite area of patch, 3= erythema plus edema beyond the area of patch), and Berger & McGorry (2001) score 1 to 7 (1 defines no skin reaction while 7 defines visible edema that starts to spread out or edema bigger than the patch area). Niacin solution was kept on the skin for no longer than 5 minutes, and the evaluation was done in five minutes intervals, up to 30 minutes after patch removal. Puri et al. (2002) attempted, together with visual inspection, to further objectify the method by a volumetric biochemical niacin flush-based index. The intensity of skin flushing after the application of solutions containing four different niacin concentrations was monitored continuously for 20 minutes. Smesny et al. (2001) were the first

to quantify skin erythema following niacin application by optical reflection spectroscopy (a simple and quick method for the quantification of colour intensity, suitable for the determination of changes in skin reddening due to local vasodilatation). This method was applied in their latter studies (Smesny et al. 2003, 2004, 2005, 2007). Messamore et al. (2003) evaluated the vasodilatory effect on the skin after applying a niacin solution (alpha-methyl nicotinate - AMN) by laser Doppler flowmetry (a method of non-invasive, continuous measurement of microcirculation), and found a significant difference between schizophrenic patients and healthy controls. EC_{50} (the molar concentration of an agonist, which produces 50% of the maximum possible response for that agonist) for AMN was significantly elevated in the schizophrenia group. Based on these results the authors suggested reduced pharmacological sensitivity to niacin in schizophrenia patients i.e. abnormalities in enzymes, receptors, or signal transduction mechanisms that affect synthesis, release, or response to vasodilatory prostaglandins.

There are a number of factors that may modify the intensity of niacin response: concentration of applied solutions, duration of exposure, duration of evaluation, as well as methods for evaluation of test results. Smesny et al. (2003) established an important interaction of the niacin concentration and time of evaluation (i.e. time elapsed since the beginning of patch application) in patients having their first psychotic episode ($p<0.001$), using two different methods of evaluation (visual inspection and optical reflection spectroscopy). Cyhlarova et al. (2007) obtained the same results while testing niacin response in dyslexic patients. Tavares et al. (2003) also observed the combined effect of concentration and time. In their study, significant differentiation between schizophrenic patients and healthy controls was achieved only with 0.001M concentration of niacin at time intervals of 10, 25 and 30 minutes from the beginning of the application. Cychlarova et al. (2007) applied the niacin patch for 60 seconds; Smesny et al. (2005) applied it for 90 seconds, while in most of the other studies the niacin patch was removed after 5 minutes (Ward et al. 1998, van Haandel et al. 2006, Liu et al. 2007). As far as the duration of evaluation is concerned, Ward et al. (1998) established the differentiation between test and control subjects by scoring the redness after niacin solutions were applied for five minutes, and then removed. Smesny et al. (2003) established significant differentiation between investigated groups 11 minutes, and Puri et al. (2001) 15 minutes after patch removal. The method of skin erythema evaluation may further influence the results of niacin testing. That is why Smesny et al. (2003) combined two methods of niacin response verification: visualization by scoring the intensity of response at the 1-7 scale (Berger & McGorry 2001), and optical reflection spectroscopy, to obtain best validity of the results. When only erythema, but no edema was present, the two methods were in good correlation, but with the development of edema that appeared earlier when higher concentrations (0.1M and 0.01M) were applied, the verification of erythema by optical reflection spectroscopy was impaired, and only the descriptive visual method enabled successful differentiation between the two groups of subjects. The recent study of Kerr et al. (2008) revealed excellent inter- and intra-rater reliability of the 12-min topical niacin test sensitivity using visual evaluation (7-point descriptive scale) and the calculation of the niacin sensitivity score. Four different concentrations of the niacin solution were simultaneously applied (0.1 M; 0.01 M; 0.001M; 0.0001M) and rated at four time-points (3-min intervals) by three independent raters.

Prior to niacin sensitivity testing, medical examination and history taking is necessary in order to establish the disease and relevant pharmacotherapy that might skew the results of the niacin test. Individuals suffering from skin conditions and/or diseases (eczema, psoriasis) were usually excluded from testing (Ward et al. 1998, Smesny et al. 2005, Smesny et al. 2007) as well as those individuals who recently have used non-steroid anti-inflammatory drugs (Ward et al. 1998, Nilsson et al. 2006) since they might interfere with prostaglandin synthesis (inhibition of the cyclooxygenase-2).

THE RESULTS OF STUDIES OF NIACIN SENSITIVITY IN PATIENTS WITH SCHIZOPHRENIA AND OTHER PATIENTS

Many studies have investigated altered skin response to niacin in patients with schizophrenia (Table 1). Results of niacin testing were used as a potential marker of PUFAs deficiency, therefore

also of impaired membrane phospholipid metabolism. Attenuated or absent skin flushing in patients with schizophrenia was explained by a deficit in the synthesis of prostaglandins (Feldberg 1976, Horrobin 1977). Therefore, Horrobin (1980) proposed the niacin test as an objective biochemical diagnostic parameter. After delineation of the impact of the fatty acid content and altered phospholipid metabolism to physiological roles of cellular membranes (receptor function and signal transduction), the membrane phospholipid hypothesis in the etiology of schizophrenia emerged (Horrobin 1998). Evidence for altered phospholipid metabolism in schizophrenia includes: i) increased activity of PLA2 enzyme, pivotal for deacylation of phospholipid molecules and the release of fatty acids, was found in serum, plasma, blood cells and brain tissue of schizophrenic patients (Gattaz et al. 1987, Ross et al. 1997, Barbosa et al. 2007); ii) reduced level of PUFAs (particularly AA and DHA that are abundant in the central nervous system) in the peripheral cell membranes of patients with schizophrenia (Mahadik et al. 1994, Peet et al. 1998, Arvindakshan et al. 2003); iii) nuclear magnetic resonance images of untreated patients indicated an increase in the nervous cell's membrane phospholipid disintegration (Pettegrew et al. 1991, Williamson et al. 1996, Peet 2002).

In two studies there was complete absence of skin flushing in both patients with schizophrenia and healthy controls, probably because low, insufficient oral doses of niacin were taken (25 mg and 100 mg) (Wilson & Douglass 1986, Fiedler et al. 1986). In a study by Fiedler et al. (1986) alcoholics in abstinence were also tested, but they too displayed no response to niacin . Tavares et al. (2003) found a difference in skin response between patients with schizophrenia and healthy controls, but less than in some previous studies (skin flushing response after niacin priming was absent in only 23% of patients with schizophrenia and in 14% of healthy controls). Nilsson et al. (2006), found no significant difference in skin response between the groups following oral niacin application, but measurements of the skin and body temperature revealed a delay of peak response in the diseased subjects, which was a consequence of the delayed vasodilatatory response. Niacin testing was also conducted in healthy relatives of patients with schizophrenia (Waldo 1999, Shah et al. 1999, Nikolov et al. 2002, Lin et al. 2007, Smesny et al. 2007), and in patients experiencing the first psychotic episode that met criteria for schizophrenia-like psychosis (Table 1) (Smesny et al. 2003, 2005); the results were contradictory. While some studies reported a significantly weaker niacin–induced skin response in the first line relatives of patients with schizophrenia than in healthy controls (Waldo 1999, Shah et al. 1999, Lin et al. 2007), other studies did not find significant differences (Nikolov et al. 2002, Smesny et al. 2007). Smesny et al. (2003) compared the niacin–induced skin response in first-episode patients and controls and found a significantly weaker niacin response in patients. A later study by Smesny et al. (2005) that included both first-episode and chronic patients with schizophrenia , and their age and gender matched healthy controls, found no group difference between the skin response of first-episode and chronically ill patients. The difference in the skin response was significant between first-episode patients and controls. At the same time, the difference between the chronically ill and the control groups was not due to the less intense skin response in the age-matched control individuals.

Tavares et al. (2001) found a weaker niacin–induced skin response in unipolar depression patients than in healthy controls, although the difference was not statistically significant. In their study Rybakowski & Weterle (1991) found the delayed vasodilatatory response following niacin application, although erythema appeared in 100% of depressive patients. Bosvel van Haandel et al. (2006) found no statistically significant difference in the niacin–induced skin response between depressive patients and healthy controls. Hudson et al. (1997), Maclean et al. (2003), Liu et al. (2007) tested bipolar disorder patients, and only Maclean et al. (2003) found a weaker skin response in bipolar disorder patients; on the contrary, Hudson et al. (1997), reported a stronger niacin–induced skin response in their bipolar patients. Puri & Singh (2002) in their autism study found no statistically significant difference in the skin erythema intensity between autistic subjects and healthy controls, while the studies on dyslexic patients (Cychlarova et al. 2007), social phobia (Katzman et al. 2003), and Huntington disease patients (Puri, 2001) reported a significantly weaker niacin–induced skin response when compared to healthy controls, although to a lesser extent than in schizophrenic patients (Table 2).

Table 1. Summary of niacin skin-flush studies in schizophrenia, first psychosis, bipolar disorder and major depression

Method of evaluation	Patients diagnosis	N	Cont. N	Dose	Application[d]	Niacin response - absent or diminished skin-flushing	Reference
visual inspection	SCH	-	-	3 g	oral	no quantification	Hoffer 1962
	SCH	-	-	250 mg	oral	in about 80% of SCH	Horrobin 1980
	SCH	126	-	200 mg	oral	52% of SCH	Glen et al. 1996
	SCH major depression	33 18	- -	200 mg	oral	24% SCH, 0% depressed patients	Rybakowski & Weterle 1991
	SCH[a]	35	22	10^{-4}-10^{-1} M	local	83% SCH; 23% controls; at 10^{-2} M; p<0.0001	Ward et al. 1998
	SCH[a] major depression[a]	16 17	16	10^{-1} M	local	p=0.0085 no significant difference	Bosveld-van Haandel et al. 2006
	SCH medicated[a] SCH unmedicated[a]	32 24	18	10^{-4}-10^{-1} M	local	significant in both SCH groups at 10^{-3}-10^{-1} M	Shah et al. 2000
	SCH[a]	21	20	10^{-4}-10^{-1} M	local	90% SCH; 25% controls; at 10^{-3} M; p<0.0001	Puri et al. 2001
	SCH[a] BPD[a]	61 18	40	10^{-3}-10^{-1} M	local	49.2% SCH; 11.1% BPD; 7.5% controls; after 10 min, at 10^{-2} M; p<0.001	Liu et al. 2007
	SCH	30	17	200 mg	oral	no significant difference	Nilsson et al. 2006
	first psychosis[b]	25	25	10^{-4}-10^{-1} M	local	significant difference at all conc.	Smesny et al. 2003
	1st degree relatives of SCH patients[a]	20	-	10^{-4}-10^{-1} M	local	40% of subjects	Waldo 1999
	SCH[a] 1st degree relatives[a]	153 287	94	10^{-3}-10^{-1} M	local	p<0.05 after 5 min and after 10 min at 10^{-2} M (df=2)	Lin et al. 2007
	SCH–simplex fam.[a,e] SCH-multiplex fam.[a,f]	176 311	-	10^{-3}-10^{-1} M	local	p<0.006 at 10^{-1} M after 5-15 min	Chang et al. 2009
	SCH–simplex fam.[a,e] SCH-multiplex fam.[a,f]	176 311	94 94				
skin temp.	SCH	9	8	25 mg	oral	no significant difference	Fiedler et al. 1986
	SCHunipolar depression	33 18	-	200 mg	oral	delayed response in both groups	Rybakowski & Weterle 1991
PP[c] of earlobe skin	SCH	16	18	100 mg	oral	no significant difference	Wilson & Douglas 1986
thermal index	SCH BPD	28 18	28	200 mg	oral	42.9% SCH; 6% BPD; 0% controls; p<0.0001	Hudson et al. 1997
	SCH	23	30	200 mg	oral	43% SCH; 3% controls; p<0.01	Hudson et al. 1999
	SCH	30	17	200 mg	oral	delayed response; p=0.002	Nilsson et al. 2006
volumetric niacin response	SCH	27	26	10^{-4}-10^{-1} M	local	p=0.0037 for total skin response (at all conc.)	Puri et al. 2002
	SCH BPD	23 20	34	10^{-3}-10^{-1} M	local	p< 0.05 at all conc. after 5-20 min p<0.05 at 10^{-3} M after 5-20 min	Maclean et al. 2003
optical reflection spectro-scopy	first psychosis	25	25	10^{-4}-10^{-1} M	local	p=0.013 at 10^{-4}; p<0.001 at 10^{-3} M	Smesny et al. 2003
	first psychosis	32	32	10^{-3}-10^{-1} M	local	p<0.05 at all conc. after 3, 6, and 9 min	Smesny et al. 2005
	multiepisode SCH	32	32	10^{-3}-10^{-1} M	local	no significant difference	
	SCH 1st degree relatives	19 21	19 21	10^{-3}-10^{-1} M	local	p<0.05 at all conc. after 3, 6, and 9 min no significant difference	Smesny et al. 2007a
Laser Doppler flowmetry	SCH	27	21	10^{-5}-10^{-1} M	local	p<10^{-5} for log(EC_{50})	Messamore et al. 2003
	SCH BPD	27 26	32	0-10^{-2} M	local	p<0.0001 at 10^{-3} M; p<0.01 at 10^{-2} M no significant difference	Ross et al. 2004

[a] score 0-3; [b] score 1-7; [c] PP- photoplethysmography; [d] orally applied niacin, locally applied methyl nicotinate; [e] simplex fam. – family with only one member affected with schizophrenia; [f] multiplex fam. – family having a sib-pair with schizophrenia; SCH –schizophrenia; BPD – bipolar disorder

Table 2. Summary of niacin skin-flush studies in other neuropsychiatric diseases and healthy individuals

Method of evaluation	Patients diagnosis	N	Cont. N	Dose	Application[d]	Niacin response - absent or diminished skin-flushing	Reference
visual inspection	dyslexia	51	45	10^{-4}-10^{-1} M	local	$p<0.01$ at 10^{-4} after 9 min	Cyhlarova et al. 2007
volumetric niacin resp.	Huntington disease	6	14	10^{-4}-10^{-1} M	local	$p=0.004$ for total skin response (at all conc.)	Puri 2001
	autism	8	16	10^{-4}-10^{-1} M	local	no significant difference	Puri & Singh 2002
optical reflection spectroscopy	healthy individuals	-	63 males 54 females	10^{-3}-10^{-1} M	local	females reacted stronger than males $p<0.01$ at 10^{-3} M after 6-15 min; $p<0.05$ at 10^{-2}-10^{-1} M after 6 min	Smesny et al. 2004
laser Doppler flowmetry	social phobia	31	41	0 - 10^{-2} M	local	$p<0.05$ at 10^{-3}-10^{-2} M	Katzman et al. 2003

[a] score 1-7

EFFECTS OF ENVIRONMENTAL FACTORS, AGE AND SEX ON NIACIN–INDUCED RESPONSE

It is well known that schizophrenic patients consume significantly more nicotine than the healthy population (Leonard et al. 2007, Kohnomi et al. 2009). The consequence of nicotine smoking is creation of free radicals that reduce the level of PUFAs in membrane phospholipids (Thomas, 2000). It has been proved that nicotine intake may induce (Sastry & Hemontolor 1998), but also inhibit (Marin et al. 1997) the activity of PLA2. Different effects of tobacco smoking on the levels of membrane PUFAs are related to the stage of illness (acute or chronic), the type of therapy and the length of tobacco smoking (Reddy et al. 2004). Although a number of studies have investigated possible effects of tobacco smoking on the results of the niacin test (Mills et al. 1997, Shah et al. 2000, Smesny et al. 2005, Liu et al. 2007), none of them has established a significant effect of tobacco consumption. Hibbeln et al. (2003) established a link between tobacco smoking habit and type of diet in the patients; they found that schizophrenic patients who were smokers consumed significantly less LA than non-smoking schizophrenic patients. Non-smoking female patients consumed more DHA than male patients, whether smokers or not. The use of cannabis (Smesny et al. 2003, 2005, 2007a,b), coffee and alcohol (Lin et al. 2007) had no significant effect on the intensity of niacin response in subjects with schizophrenia but it had been shown that regular use of cannabis in healthy individuals significantly reduced the niacin response (Smesny et al. 2007b). Considering the suggested modulation of AA metabolic cascade by cannabis, the fact that there is no effect of cannabis in schizophrenic patients may indicate an already existing metabolic disorder.

Studies on the effects of antipsychotic drugs on the results of the niacin test have yielded contradictory results. While the majority of the studies reported no influence of antipsychotic drugs on niacin sensitivity (Hudson et al. 1997, Shah et al. 2000, Messamore et al. 2003, Ross et al. 2004), only the study of Tavares et al. (2003) revealed a possibility that antipsychotic drugs might alter niacin response in a proportion of patients undergoing treatment. His group reported a significant reduction of phospholipase A_2 activity after 8 weeks of treatment, as well as a conversion of a negative niacin test into positive in 30% of schizophrenic patients. Furthermore, there is evidence that prolonged use of atypical antipsychotics, mood-stabilizers, and antidepressant drugs affect similar targets suppressing common biochemical pathway(s) such as the phosphoinositide-protein kinase (PI-PKC) (McNamara et al. 2006) and ERK1/2 pathways (Thomas et al. 2006) which both involve cytosolic PLA2s. These results indicate that the niacin test might reveal balance/imbalance of membrane phospholipid metabolism and serve as a marker of the patient's response to psychopharmacotherapy, and consequently predict the odds for remission of the disease. There is a need for further systematic investigation on possible effects of a prolonged use

of antipsychotics on the niacin-induced skin flushing in schizophrenic patients, especially in terms of monitoring different stages of the illness (Smesny et al. 2005).

There is no evidence that corticosteroids, acetylcholine and histamine receptor blockers or local anesthetics such as procaine have an effect on the skin response to niacin (Wilkin et al. 1985, Messamore 2003). On the other hand, a number of studies indicate that the dietary addition of PUFAs, such as AA and DHA that cannot be synthesized *de novo* in the human body, may influence the niacin response by increasing the amount of substrate for prostaglandins synthesis (Fenton et al. 2000, Peet et al. 2001, Emsley et al. 2002).

The studies of Smesny et al. (2001, 2004) recommended a consideration of age and sex in clinical studies on niacin sensitivity. The skin niacin response diminished with age in both sexes (although recognizable at different concentrations of the niacin solution), and male sex showed a weaker niacin response than female. The effect of sex was most pronounced at the lowest niacin concentration (0.001M). The authors indicated possible effects of sex hormones on vasomotor functions and prostaglandin metabolism, but also sex-specific variation in skin anatomy or changes of skin pigmentation with age that could influence the visualisation of niacin-induced redness. The differences in pharmacodynamic responses and cutaneous penetration were observed between black and white races in the study by Berardesca & Maibach (1990).

NIACIN SKIN FLUSHING AND GENETIC LOADING IN SCHIZOPHRENIA

A number of studies have found a diminished niacin-induced skin response in the first-degree relatives of patients with schizophrenia (Waldo 1999, Shah et al. 1999, Lin et al. 2007, Chang et al. 2009) indicating that they might have a disturbance in the metabolism of phospholipids. The study by Chang et al. (2009) included the largest number of patients with schizophrenia and their first relatives. Using visualization methods they found a significantly weaker niacin response in patients where more relatives also had schizophrenia (multiplex families), than in subjects from families with only one patient with schizophrenia (simplex families) (Table 1). Furthermore, niacin testing significantly differentiated between patients from simplex families, and control individuals (Chang et al. 2009). The authors observed the same pattern of niacin response also in the 1st degree relatives (parents and siblings) of patients with schizophrenia from multiplex families, compared to simplex families, and controls (data not presented in Table 1), suggesting a high genetic loading in the niacin skin response and etiology of this multifactorial disease. The estimated heritability in their study ranged from 47% to 54%. However, the study of Smesny et al. (2007a) did not find evidence of niacin hyposensitivty as a heritability trait in schizophrenia (attenuated skin flushing was observed in 19 first-episode schizophrenic patients, but not in their 21 first-degree relatives). Although the sample of Smesny et al. (2007a) was quite small to provide relevant conclusions, it should be pointed out that the two studies used different methods of skin redness evaluation. The results of Chang et al. (2009) strongly support the hypothesis of the abnormal niacin-induced skin flush response as a marker for genetic susceptibility to schizophrenia.

DISCUSSION

Attenuated niacin skin flushing is a robust finding in schizophrenia (Table 1). In a number of studies, following local application, the niacin-induced response was evaluated by methods that showed similar informative potential. A weak or absent response to niacin has been observed in neuropsychiatric conditions other than schizophrenia. Therefore, a weak or absent response to niacin cannot represent a reliable diagnostic test for schizophrenia. Nevertheless, the niacin response is significantly weaker in schizophrenic patients when compared to bipolar or depressive (unipolar) patients (Maclean et al. 2003, Bosveld-van Haandel et al. 2006, Liu et al. 2007). The significance of this collection of data might be that in patients having their first psychotic episode, especially in adolescents and young adults, an attenuated niacin response in combination with psychotic behavior my be considered likely to suffer from schizophrenia (Ward et al. 1998). Different niacin response in schizophrenic and bipolar patients suggests the existence of biochemical differences in spite of an overlap of clinical symptoms for these two diseases. Consequently, the niacin test might help

in the differentiation of schizophrenia and other psychotic diseases. A reduced volumetric niacin response was further observed to parallel higher cerebral energy metabolism in violently offending patients with schizophrenia, leading to the suggestion of an association between lower niacin response and severity of illness (Puri et al. 2007).

Several studies have investigated a correlation between clinical symptoms and niacin insensitivity in schizophrenia (Maclean et al. 2003, Smesny et al. 2003, Smesny et al. 2005, Smesny et al. 2007). Only a study by Smesny et al. (2003) found a cluster of weak correlations between Brief Psychiatric Rating Scale (BPRS) sub-scores and visual ratings of skin redness at different niacin concentrations, although the significance values were not corrected for multiple testing. Spectroscopic results obtained by Smesny et al. (2003) showed significant correlations with total PANSS score and PANSS negative sub-score for 0.01M niacin solution.

Since attenuated niacin flushing in schizophrenia additionally showed a high genetic loading (Lin et al. 2007, Chang et al. 2009), there was a possibility that diminished or absent niacin flushing represented an intrinsic feature and endophenotypic marker in schizophrenic patients. The results actually suggest that there was a phenotypic subpopulation within the population of schizophrenia sufferers that displayed disturbed membrane phospholipids metabolism, and the niacin test might be important in the identification of this subpopulation (Tavares et al. 2003). Glen et al. (1996) and Maclean et al. (2003), although with contradictory observations, were the only ones that investigated the correlation between the niacin test, disturbed phospholipid metabolism and schizophrenia. While Glen et al. (1996) reported that schizophrenic patients with a weak or absent skin flushing following niacin application had reduced levels of AA and DHA in peripheral cell membranes, Maclean et al. (2003) did not find evidence for an association between a reduced or weak niacin response in patients with schizophrenia and any fatty acid deficiency.

The studies by Ross (2003) and Smesny et al. (2005) considered the niacin test as supportive, although not conclusive for the membrane phospholipid hypothesis of the etiology of schizophrenia. Disturbance in the prostaglandin signaling cascade may not be necessarily caused by PUFA precursor's deficit. The cause may be at the level of niacin receptors, or prostaglandin receptors in the blood vessel wall, as well as in poor vasomotor activity. A recent *postmortem* finding of a reduced expression of high-affinity niacin receptor HM74A in the anterior cingulate cortex of individuals with schizophrenia suggests possible mechanisms for attenuated niacin skin flushing in this illness (Miller & Dulay 2008).

Genetic studies might help in elucidating the individual niacin sensitivity. According to our knowledge, only one study investigated the association between the niacin skin response and genotype (Covault et al. 2004). The authors found greater dermal erythema following topical application of methyl-nicotinate in patients with a T allele of the functional C/T polymorphism in the first introne of the X-linked FACL4 gene (long-chain fatty acid-CoA ligase type 4; Xq22.3). Facl4 enzyme selectively esterifies AA, DHA and eicosapentaenoic acid (EPA) with co-enzyme A, forming acyl-CoA, which could be incorporated into membrane phospholipids. A statistically significant excess of the T allele was found in 198 subjects with major depression. An excess of the T allele, although not significant, was also found in 58 schizophrenic subjects, while in 70 alcoholics no difference was found in comparison to 229 controls.

CONCLUSIONS

New biochemical and genetic studies on patients with schizophrenia, as well as on other psychiatric and neurological patients are needed in order to elucidate underlying mechanisms of the attenuated skin response to niacin. The importance of genetic factors or psychopharmacotherapy in skin (in)sensitivity should also be established. It is necessary to establish a unique testing and evaluation method, providing thus for comparability of all the study results; age, sex and environmental factors (drug abuse, medication, diet) should be stringently controlled.

By comparing different evaluation methods of the niacin-induced skin response and the results they yielded (Table 1) we concluded that visual inspection is a satisfactory, non-invasive, fast, simple, reproducible and cheap method, capable of differentiating groups of tested subjects after the application of different concentrations of niacin solutions (from 10^{-4} to 10^{-1} M). The concentration of niacin that yielded best differentiation among

groups of tested subjects was, in the majority of studies 10^{-3}-10^{-2} M, while recommended duration of evaluation of the results was 5-20 minutes in 3-5 minute intervals. The niacin test suggests to the patient that her/his disease is biochemical, which can contribute to the development of a positive attitude towards medication.

Based on the reviewed results we concluded that niacin (in)sensitivity might be an important research tool primarily in schizophrenia, but possibly also in other psychiatric and neurological diseases. New research is necessary to establish whether the niacin skin flush test could serve as a diagnostic marker used as an auxiliary method, together with the existing diagnostic criteria, and for follow-up of the psychic (and/or biochemical) status of patients (i.e. at admission and during pharmacotherapy evaluation).

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