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ScienceDirect
Psychiatry Research 152 (2007) 181–187
PSYCHIATRY RESEARCH
www.elsevier.com/locate/psychres

Absent response to niacin skin patch is specific to schizophrenia and independent of smoking

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Received 20 July 2005; received in revised form 3 July 2006; accepted 2 October 2006

Abstract

This study investigated the differences in niacin skin flush responses between patients with schizophrenia, bipolar mania, and normal controls. We applied niacin patches of three concentrations (0.001 M, 0.01 M, and 0.1 M) to the skin of 61 patients with schizophrenia, 18 patients with bipolar mania, and 40 normal controls for 5 min. Flush responses were rated at 5, 10 and 15 min after application. Flush responses were significantly different among three groups at the concentrations of 0.1 M and 0.01 M at all of the three rating time points. The use of nicotine did not have significant influences on the flush responses. Absent response was significantly more prevalent in the schizophrenia group than in the other two groups, but was not significantly different between the bipolar and the control group. The greatest degree of differentiation in flush responses among groups occurred at the 0.01 M concentration, and the rating time point of 10 min with 49.2% of schizophrenic patients but only 7.5% of controls and 11.1% of bipolar patients not showing a flush response. The niacin skin test for schizophrenia had 49.2% sensitivity and 92.5% specificity compared with controls. This study found that absent response to niacin skin patch was specific to schizophrenia and independent of smoking status.

Keywords: Schizophrenia; Bipolar affective disorder; Niacin skin patch; Nicotine use

1. Introduction

Flushing of the face and trunk has been reported in 92% to 100% of patients receiving oral nicotinic acid treatment for hyperlipidemia (Mosher, 1970). The vasodilatory response was caused by stimulating the release of prostaglandin (PG), in particular, PGD2 from the skin (Morrow et al., 1989, 1992). Absent or diminished flush

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doi:10.1016/j.psychres.2006.10.002

responses in schizophrenic patients after niacin intake was first reported by Hoffer (1962) and was proposed as a possible simple biochemical test for schizophrenia by Horrobin (1980). Although two subsequent studies failed to replicate these findings (Fiedler et al., 1986; Wilson and Douglass, 1986), this has been attributed to using too low a dose of NA (Hudson et al., 1997). However, using a higher 200 mg dose of NA, Rybakowski and Weterle (1991) and Hudson et al. (1997, 1999) reported that approximately 25–40% of schizophrenic patients showed no vasodilatory response.

Ward et al. (1998) observed a diminished flush response to topically applied methyl nicotinate in about 83% of schizophrenic patients using visual inspection for assessment of flush responses. Several follow-up studies using the same method also demonstrated impairment to topically applied methyl nicotinate in schizophrenic patients, though the proportion of impairment was not so high (Shah et al., 2000; Puri et al., 2001, 2002; Maclean et al., 2003). One study failed to show a significantly higher prevalence for absent flush responses to topical niacin in schizophrenic patients (Tavares et al., 2003). The studies using other methods for assessment of flush responses also revealed significantly diminished flush responses in schizophrenic patients, including those using laser Doppler flowmetry (Messamore et al., 2003; Ross et al., 2004a) and those using optical reflection spectroscopy (Smesny et al., 2001, 2003, 2005).

Whether the abnormal skin flush response to niacin is present only in schizophrenic patients, and not in bipolar patients, remains unclear. Bipolar patients were reported to have either an accentuated flush response to oral NA (Hudson et al., 1997) or an attenuated response to topical methyl nicotinate (Maclean et al., 2003). In addition, a significantly higher prevalence of cigarette smoking was present in schizophrenia than in the normal population (Hughes et al., 1986; Fowler et al., 1998). A possible effect of nicotine on niacin response was first considered by Vaddadi (1981) due to the similarity of niacin and nicotine. Therefore, its possible confounding effect upon the abnormal niacin skin flush in schizophrenia should be considered.

The samples of the above studies come mainly from Caucasian subjects. It is unclear if the phenomenon of diminished responses to niacin skin patch in schizophrenic patients is also present in the samples of different ethnic background.

This study investigated the differences in niacin skin flush responses between patients with schizophrenia, bipolar affective disorder, and normal controls, and it also examined the confounding effect of smoking on niacin skin flush responses in a sample of ethnic background other than Caucasian.

2. Methods

2.1. Subjects

Three groups of subjects, schizophrenic patients, bipolar manic patients, and healthy controls, were recruited. All subjects were required to meet the inclusion criteria of no past history of drug and food allergy, no major systemic illness (especially heart disease, autoimmune disease, and severe allergic disease such as asthma and severe skin allergic disease), and no use of steroid and non-steroid anti-inflammatory drugs within a week before niacin skin test. Sixty-one patients who met the DSM-IV criteria for schizophrenia were recruited from either the acute psychiatric ward or the day care unit of the National Taiwan University Hospital. Eighteen patients who met the DSM-IV criteria for bipolar I disorder, most recent episode manic, were recruited from the acute psychiatric ward. Patients with schizophrenia were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and those with bipolar mania were assessed on the Young Mania Rating Scale (YMRS) (Young et al., 1978). Forty healthy controls were recruited from the hospital staff through a brief interview to rule out a history of major psychiatric disorders. After informed written consent was given, data collection began and skin tests were performed. Data on clinical variables and smoking history were collected from the interview with the patients and controls and from medical charts.

Table 1 shows the demographic characteristics, psychopathological ratings, medication status and cigarette smoking in the three study groups. There are no significant differences in age and sex, but the prevalence of current smoking and the quantity of smoking in pack-year in the schizophrenic group are significantly higher than those of the other two groups. The durations of illness of schizophrenic and manic patients are relatively long. Five schizophrenic patients and four manic patients are in their first episode, and most of them are in multi-episode courses. The PANSS scores of schizophrenic patients reveal that they have a mild to moderate severity of illness. The YMRS scores of manic patients reveal that they are in the manic state. All of the schizophrenic patients received neuroleptic medication and two-thirds of them received atypical antipsychotics, including risperidone, olanzapine, zotepine, quetiapine, ziprasidone, and clozapine. The manic patients received mood stabilizers, neuroleptics or two combined.

Table 1
Comparison of demographic characteristics, psychopathological ratings, medication status and cigarette smoking among the three study groups

Disease group	Schizophrenia (n=61)	Bipolar mania (n=18)	Controls (n=40)
Gender (male/female)	37/24	8/10	17/23
Age (years)	33.2±9.4	29.2±11.4	29.3±9.3
Duration of illness (years)	9.6±8.2	8.0±7.2	–
Current smoker [a]	27 (44.3%)	3 (16.7%)	4 (10%)
Smoking quantity (pack-year) [b]	7.5±16.1	1.3±3.9	0.5±1.8
PANSS total	56.7±14.4	–	–
YRMS total	–	24.6±9.8	–
Neuroleptics (atypical/typical)	42/19	8/3	–
Mood stabilizers (lithium/carbamazepine/valproic acid)	0/3/0	9/2/5	–

[a] χ^2=15.37, df=2, P<0.001 by chi-square test.
[b] $F_{2,\ 116}$=4.929, P<0.01 by one-way ANOVA.

2.2. Niacin skin test

We used a modified protocol as that in Ward et al. (1998). We found that in the concentration of 0.0001 M methyl nicotinate, there was nearly no flush response even in the normal control and bipolar group and that at the 20-min time point, the flush responses were not different from that at the 15-min time point in our preliminary study. Therefore, we used three concentrations and three measurement intervals instead. Skin patches of blank and three concentrations (0.001 M, 0.01 M, 0.1 M) of aqueous methyl nicotinate (AMN) were topically applied to the forearm skin of all the subjects for 5 min. The patches were then removed and pictures were taken with a digital camera at 5, 10 and 15 min after application. The degree of flush response was rated from the pictures using the following criteria; 0: no erythema; 1: incomplete erythema; 2: complete erythema; 3: erythema plus edema (Ward et al., 1998). The two authors (C-M, L and S-S, C) who were blinded to the diagnostic groups rated the pictures. Inter-rater reliability was calculated based on the results of rating 50 pictures independently, using intra-class correlation coefficients (ICC). The ICC values were 0.85–0.94 at different concentrations of niacin, and the reliability of skin response assessment was thus judged to be satisfactory.

2.3. Statistical analysis

Differences in the mean age and quantity of smoking in pack-year among groups were examined using one-way analysis of variance (ANOVA). The gender and prevalence of current smokers were compared among the groups by chi-square test. The initial analyses of flushing data started with a repeated measures three-way ANOVA with TIME (5, 10, 15 min) and CONCENTRATION (0.001 M, 0.01 M, 0.1 M) as within-subject factors and DISEASE (SCH, BAD, NC) as the between-subjects factor. SMOKING (cigarette smoking in pack-year), NEUROLEPTICS (typical or atypical neuroleptics use), and MOOD STABILIZER (Lithium, Carbamazepine, and Valproic acid use) were used as covariables. Subsequent to this complex ANOVA, additional ANOVAs were calculated for subgroups if a significant interaction exists between any two of the three factors. For repeated measure ANOVAs, a Greenhouse–Geisser correction was performed where necessary and is indicated in the text by quotation of an ε value. For an easier understanding, only uncorrected degrees of freedom are reported.

For assessment of the prevalence of absent responses, we defined response with flush scores of 2 and 3 as normal, and scores of 0 and 1 as an absent response as Tavares et al. (2003) did. The difference in the prevalence of absent response among the study groups was analyzed by chi-square test. All statistical analyses were performed using SPSS for Windows version 11.0.

3. Results

The initial ANOVA including all data revealed a significant interaction between DISEASE and CONCENTRATION ($F_{4,\ 232}$=11.2, P<0.001, ε=0.801), indicating that the differences of flush responses among three disease groups depend on the methyl nicotinate concentrations used. Subsequent repeated measures two-way ANOVA with TIME as the within-subject factor and DISEASE as the between-subjects factor under three concentrations revealed significant main effects of DISEASE at the concentrations of 0.1 M ($F_{2,\ 116}$=11.3, P<0.001) and 0.01 M ($F_{2,\ 116}$=14.4, P<0.001), and post-hoc comparison revealed the flush response of the schizophrenic group is significantly lower than that of the other two groups, and the flush response of the bipolar and control groups is not significantly different. Under the concentration of 0.001 M, the main effect of DISEASE is not significant ($F_{2,\ 116}$=2.2, P>0.05), indicating that there are no differences among the three groups. The effects of the covariables SMOKING, NEUROLEPTICS, and MOOD STABILIZER are not significant under all concentrations. The flushing scores of the three disease groups with the measurement intervals under the concentrations of 0.01 M and 0.1 M are plotted in Fig. 1. None of the scores of the positive, negative, and general subscales of the PANSS

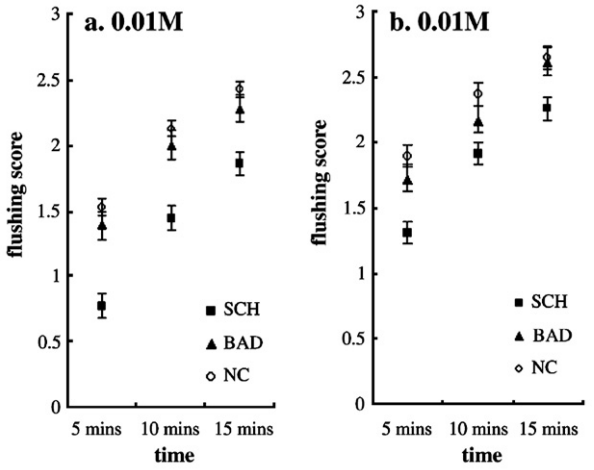

Fig. 1. The flushing scores of the three disease groups with the measurement intervals under the concentrations of 0.01 M and 0.1 M. The mean scores of the schizophrenia group are significantly lower than those of the bipolar and control groups, while the mean scores between the bipolar and control groups are non-significant at all the measurement intervals under the two concentrations.

correlates significantly with niacin response (data not shown).

Table 2 shows the prevalence of absent response in the three study groups after application of topical skin patch of three different concentrations of AMN at three time points. At the concentration of 0.001 M, there were few flush responses and nearly 100% with absent responses in all of the groups at the three time points. At the concentration of 0.1 M and 0.01 M, the prevalence of absent responses decreases with higher concentrations and longer elapsed time after application. The prevalence of absent response at the concentration of 0.01 M of AMN ranged from 21.3% to 73.8% in schizophrenia patients, 0 to 61.1% in bipolar patients, and 2.5% to 40% in controls at the different time intervals. At the concentration of 0.1 M of AMN, the prevalence ranged from 9.8% to 49.2% in schizophrenia patients, 0 to 22.2% in bipolar patients, and 2.5% to 10% in controls. Comparisons of the prevalence of absent response revealed significant differences among the three groups at concentrations of 0.1 M and 0.01 M of AMN ($P<0.005$), except for the 0.1 M concentration of AMN at the 15-min measurement interval. The test parameters that could best elicit differences in groups to enable differentiation based on niacin flush response were the 0.01 M concentration of AMN, and assessment at 10 min after the application. Under this condition, nearly 50% of schizophrenia patients, but only about 10% of bipolar patients and normal controls failed to show a niacin skin flush response. The niacin skin test for schizophrenia had 49.2% sensitivity and 92.5% specificity compared with controls under this condition.

4. Discussion

Our study results suggest that the absent response to the niacin skin patch is specific to schizophrenia and independent of nicotine use. Our study also demonstrated that the assessment of skin flush response by visual inspection using a 4-point score could be performed with satisfactory reliability, indicating its potential practical value as a clinical examination. The test parameters of niacin concentration of 0.01 M and assessment of skin response at 10 min after application were best able to differentiate schizophrenia, bipolar mania, and control groups. The sensitivity of the niacin skin test for schizophrenia was 49.2% and the specificity was 92.5%. While this test might not be a reliable diagnostic test for all schizophrenia patients due to its low sensitivity, it might be able to identify a specific subgroup of schizophrenia patients.

Our results that the flush responses to niacin skin patch increase with concentration of AMN and measurement interval are consistent with those of previous reports (Ward et al., 1998; Shah et al., 2000; Puri et al., 2001). However, the finding of very few flush responses in all three groups at the concentration of 0.001 M of AMN is different from findings in previous studies, which

Table 2
The prevalence of absent response to niacin skin patch (rating <2) in schizophrenia patients, bipolar patients, and controls at three concentrations and at three measurement time points

Time point	5 min				10 min				15 min			
	SCH[a]	BAD[a]	NC[a]	χ^2 (df=2)	SCH	BAD	NC	χ^2 (df=2)	SCH	BAD	NC	χ^2 (df=2)
Concentration	%	%	%		%	%	%		%	%	%	
0.1M	49.2	22.2	10	17.98**	21.3	0	2.5	11.06*	9.8	0	2.5	3.67
0.01M	73.8	61.1	40	11.53*	49.2	11.1	7.5	23.64**	21.3	0	2.5	11.06*
0.001M	100	100	100	–	100	100	100	–	98.4	94.4	97.5	0.87

[a]: SCH: schizophrenia group; BAD: bipolar disorder group; NC: control group.
* $P<0.005$, ** $P<0.001$ by chi-square test.

reported that the flush response was observable at this concentration (Ward et al., 1998; Shah et al., 2000; Puri et al., 2001). Possible explanations for this discrepancy include ethnic differences in niacin sensitivity or differences in percutaneous penetration, as was reported in the percutaneous penetration of nicotinates between whites and blacks (Berardesca and Maibach, 1990).

Nicotine use has no effect upon the skin response to niacin in this study. This finding is consistent with those of previous studies (Shah et al., 2000; Messamore et al., 2003; Smesny et al., 2003, 2005; Ross et al., 2004a) and with the results of the animal study using a rat model of nicotinic acid-induced vasodilation (Turenne et al., 2001).

Niacin may induce skin response via niacin receptors by localized prostaglandin (PG) synthesis and release, and resulting vasodilation of superficial skin microvessels, to result in clinically observable erythema and edema. In a quantitative dose-response study using laser Doppler flowmetry, Messamore et al. (2003) suggested that the skin flush abnormality in schizophrenia primarily reflects reduced pharmacological sensitivity to niacin rather than an inadequate cutaneous vasodilatory response to the stimulus. The components of pharmacological sensitivity to niacin have been identified recently. Dermal macrophages were identified as sites of PG production in the rat (Urade et al., 1989). The low-affinity and high-affinity receptors for nicotinic acid in humans, termed HM74 and HM74a, respectively, have been identified, and the underlying signal transduction pathway involves Gi-protein mediated c-AMP change (Soga et al., 2003; Wise et al., 2003). It has been shown that HM74 and HM74a can mediate macrophage responses to niacin via activation of the prostaglandin synthesis pathway and induction and activation of peroxisome proliferator-activated receptor-γ (PPARγ) (Knowles et al., 2006). It is likely that HM74 or HM74a is the primary receptor mediating skin flush responses to niacin. The activity of phospholipase A2 (PLA2), which cleaves phospholipid in cellular membranes into lysophospholipids and free fatty acids, a PG precursor, has been demonstrated higher in schizophrenic patients than in controls and higher in patients with absent response to niacin than in those with positive responses (Tavares et al., 2003). It indicated that a subgroup of schizophrenia manifested with diminished response to niacin may associate with abnormalities in enzymes, receptors, or signal transduction mechanisms that affect the synthesis, release, or response to vasodilatory PG.

Our data showed no significant correlations between the flush response and psychopathological ratings in schizophrenia. Smesny et al. (2003) reported the flush response was inversely correlated with the score of negative symptoms. The other studies reported no significant correlations as our study did (Maclean et al., 2003; Tavares et al., 2003; Smesny et al., 2005). Our data also showed the use of typical or atypical antipsychotics seemed to have no effect upon the niacin response, as is consistent with the findings of previous studies (Maclean et al., 2003; Ross et al., 2004a). Our data showed there were no significant differences in flush responses between the patients using clozapine ($n=7$) and those using other typical and atypical antipsychotics and did not support the observation that the patients taking clozapine have a significantly stronger skin response than those taking other typical and atypical antipsychotics (Ward et al., 2001). Shah et al. (2000) reported medicated patients showed general trends to flush less than unmedicated ones. Tavares et al. (2003) reported 4 of 13 schizophrenic patients who showed absent response to niacin skin patch showed a positive response after the antipsychotic treatment. Smesny et al. (2005) reported impaired niacin sensitivity was present in acute first episode but not in multi-episode schizophrenia, and they suggested longitudinal studies have to rule out possible long-term effects of neuroleptic medication. Therefore, it is still inconclusive for the effects of antipsychotics upon the niacin skin response.

The bipolar patients were reported to have either an accentuated flush response to oral NA (Hudson et al., 1997) or an attenuated flush response to topical methyl nicotinate (Maclean et al., 2003). Our findings that there are no significant differences in the flush responses assessed with the 4-point redness score between the bipolar and control group are inconsistent with those reported by Maclean et al. (2003), which revealed significantly diminished flush responses in bipolar patients compared with controls. We considered the following reasons for the inconsistency: First, the duration for niacin skin patch application was only 1 min in the study of Maclean et al. (2003), instead of 5 min in our study. Therefore, the ceiling effect may render the differences between bipolar patients and controls insignificant. Secondly, the method for assessment of flush responses in our study is not sensitive enough to detect small differences between the two groups. A more sensitive method for the assessment of flush responses is indicated for further study, including a 7-point assessment scale integrating time course, redness, and edema (Berger and McGorry, 2001; Berger et al., 2002; Smesny et al., 2003), laser Doppler flowmetry (Messamore et al., 2003; Ross et al., 2004a), and optical reflection spectroscopy (Smesny et al., 2001, 2003, 2005). Thirdly, though our study and that of Maclean et al. applied the niacin skin patch to bipolar

patients in the acute manic phase, the severity of our samples was greater severe than that of Maclean's sample (YMRS score: 24.6±9.8, 17±10, respectively). Another study that administered oral NA to bipolar patients in the stable phase reported an accentuated response (Hudson et al., 1997). Whether the difference in response was due to differences in the severity and phase of illness remains to be clarified.

Depressed patients had been shown either a slightly diminished response to oral and topical niacin (Rybakowski and Weterle, 1991; Tavares et al., 2001) or delayed response to oral and topical niacin (Rybakowski and Weterle, 1991; Ross et al., 2004b). Reduced response has also been noted in patients with social phobia (Katzman et al., 2003) and Huntington's disease (Puri, 2001), while normal in autism (Puri and Singh, 2002). The phenomenon of reduced response in the niacin skin test seems not specific to schizophrenia only, but whether the underlying mechanism among different disease groups is the same or not remained to be clarified.

In summary, our study showed that absent response to niacin skin patch was present in schizophrenic patients specifically, but not in bipolar manic patients, and that the flush response was independent of nicotine use. Whether the abnormal niacin flush response is a stable trait marker of schizophrenia needs further clarification.

Acknowledgements

This research was supported by the grants from the National Health Research Institute (NHRI-CN-MG-9006S; NHRI-EX93-9113PP), the National Taiwan University Hospital (NTUH-90S1562), and the NRPGM, National Science Council, Taiwan (NSC-93-3112-B-002-012).

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