Phospholipid-Arachidonate-Eicosanoid Signaling Underlying Niacin-induced Skin Flushing: A Potential Schizophrenia Endophenotype

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Schizophrenia (SZ) is a biologically complex disorder with perturbations in multiple neurochemical systems. A blunted niacin response is a physiological abnormality, which is substantially over-represented among subgroup of schizophrenia (SZ) patients, compared with healthy control (HC) and patients with bipolar disorder (BD) or major depression. Accumulating data suggest that Phospholipid-Arachidonate-Eicosanoid (PAE) pathway appears to be the biochemical mechanisms underlying the niacin-induced skin flushing. A laser Doppler flowmeter was used to quantify skin blood flow responses to a range of topical concentrations (10^{-5}–10^{-1}M) of aqueous methyl-nicotinate (AMN), a skin-permeable niacin derivative. From the dose-response curves, EC50 values (the concentration of AMN required to elicit a half-maximal blood flow response) and maximal blood flow (MBF) values were calculated for each subject. Box-whisker plots were used to show the distributions of EC50 and MBF data among SZ, BD and HC subjects. Approximately 75% of HC subjects or BD patients had EC50 values below the third-quartile (2.0 mM) whereas only 50% of SZ patients fell into this normal range. Similarly, MBF was significantly lower in SZ than in BD or HC groups. Using a combined statistical definition of: 1) EC50 above the 90th percentile of the control range (higher EC50 values indicate lower sensitivity to AMN); and 2) maximal blood flow response below the 75thpercentile for the control range, we found that a blunted niacin response predicted schizophrenia with 34% sensitivity and 97% specificity. Our data support the view that a blunted niacin response is substantially over-represented in SZ compared with BD and HC groups. The blunted niacin response appears to define a physiological subtype of SZ, presumably one characterized by abnormal PAE signaling. The current quantitative method of measuring niacin subsensitivity could lead to improved methods for early detection of the illness. The identified SZ-subtype may also be valuable in early specific treatment.

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