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ABNORMAL PHOSPHOLIPID METABOLISM IN SCHIZOPHRENIA: EVIDENCE FROM EPIDEMIOLOGICAL FINDINGS, CLINICAL OBSERVATIONS, AND PRELIMINARY CLINICAL TRIALS

Mark G. Opler [1] and Lewis A. Opler [2,3]

[1] Joseph L. Mailman School of Public Health, Columbia University, New York, New York 10032, [2] Columbia University College of Physicians and Surgeons, New York, New York 10032,[3]New York State Office of Mental Health, 1500 Waters Place, Bronx, New York 10461

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1. ABSTRACT

Both epidemiological findings and clinical observations and have shaped our thinking as regards to the neuropathology of schizophrenia. Epidemiological findings implicating environmental risk factors, including maternal dietary deficiency and urban birth place, suggest schizophrenia is a developmental disorder, whereas clinical observations gave rise to the "dopamine hypothesis." Epidemiological findings lead to complex multifactorial models, while clinical observations lead to more readily to testable, but not necessarily generalizable, hypotheses. Points where findings from these different approaches converge may provide us with new insights and points of departure. In this paper, clinical observations and epidemiological findings are presented which suggests that a subgroup of schizophrenics have abnormalities in phospholipid metabolism. Preliminary clinical trials involving administration of omega-3 fatty acids thus far appear to support this hypothesis.

2. INTRODUCTION

Different branches of science and of medicine develop unique patterns of observing, theorizing, testing, and applying. Psychiatry, possibly more than other clinical and scientific disciplines, has progressed as serendipitous clinical observation have been used to generate causal hypotheses. In part this is due to the complexity of the central nervous system; in part it is due to mental disorders being human disorders which cannot easily, if ever, be mimicked in animal models: one can create and study a diabetic cat but not a schizophrenic rat.

A serendipitous finding which transformed our conceptualization of schizophrenia was Delay and Deniker's observation in 1952 that chlorpromazine, originally thought to be just a new sedative, improved hallucinations and delusions in psychotic inpatients in Paris. They coined the term "neuroleptique" ("neuroleptic" in English), meaning a substance that grabs the nerve, because they were struck by the broad range of chlorpromazine's effects on the central nervous system: sedation, decrease in psychosis, and induction of motor side effects (1). Subsequent to their discovery, Carlsson demonstrated that neuroleptics block dopamine receptors. This lead to the dopamine hypothesis of schizophrenia, i.e., that schizophrenia is a disorder resulting from too much dopamine activity (hyperdopaminergia) (2,3).

Similarly, the concept and the diagnosis "neuroleptic-refractory" schizophrenia emerged as a result of serendipitous events. In the late 1950s, in modifying imipramine in the hopes of synthesizing new and better tricyclic antidepressants, chemists in Switzerland created clozapine (4). In preclinical behavioral trials, clozapine blocked conditioned avoidance--a predictor of antipsychotic efficacy in humans--without causing catalepsy--another predictor of antipsychotic efficacy. Today we know that induction of catalepsy, but not reversal of conditioned avoidance, also correlates with unwanted extrapyramidal side effects, including drug-induced parkinsonism and tardive dyskinesia. When administered to schizophrenics in Phase II clinical trials, clozapine treated psychotic symptoms, but, unexpectedly, did not cause

motor side effects. At least as remarkable, and also unexpected, roughly half of schizophrenics who had failed to respond to standard neuroleptics showed significant improvement on clozapine. Thus the concept of "neuroleptic-refractory" schizophrenia emerged, and in 1990 in the United States clozapine (as brand name Clozaril) was FDA approved and subsequently marketed for "the management of severely ill patients who fail to respond adequately to standard antipsychotic drug treatment." (5 (p.2155)).

Clozapine, while it does block dopamine receptors, does so less potently than all of the standard neuroleptics, and yet emerged as the only treatment for "neuroleptic-refractory" schizophrenia. Scientists noted that for clozapine the ratio of serotonin blockade to dopamine blockade was orders of magnitude higher than for the standard neuroleptics. Meltzer and colleagues proposed that it was not simply dopamine blockade but *combined* serotonin-dopamine blockade that explained clozapine's remarkable clinical profile (6). This had two results: first, the pharmaceutical industry began to develop and market other combined serotonin-dopamine antagonists; and, second, the scientific community began to conceptualize schizophrenia as a disorder of both dopamine and serotonin circuitry.

In the United States, four new antipsychotics have been introduced, all combined serotonin-dopamine antagonists: risperidone, olanzapine, quetiapine, and ziprasidone. While all four cause less motor side effects than the older standard neuroleptics (although none is quite as "clean" in this regard as clozapine), none have been shown to be effective and none have been approved for use in neuroleptic-refractory schizophrenia.

Chlorpromazine and the other standard neuroleptics, and, more recently clozapine and the other new antipsychotics, have already helped millions of patients while advancing our understanding of schizophrenia. But there still remains a large group of schizophrenics who respond only to clozapine, not to the other serotonin-dopamine antagonists, while other schizophrenics do not respond to any of our presently available treatments. This suggests that while abnormalities in both the dopamine and serotonin systems may explain some of the dysfunction found in schizophrenia, abnormalities in these two systems alone does not explain adequately the neuropathology underlying schizophrenia (7).

The convergence of epidemiological findings and clinical observations suggest that schizophrenia may, in part, involve abnormalities in phospholipid metabolism, as summarized below.

3. EPIDEMIOLOGIC FINDINGS

There is a long-standing and highly replicable finding that identical twins have a 50% concordance rate for schizophrenia, i.e. in identical twin pairs where one is schizophrenic, there is a 50% chance that the other twin will also have the disease. In contrast, amongst other siblings, including non-identical twins, the concordance rate is 10%. While this finding supports the hypothesis that familial, and probably genetic, factors contribute to the risk of developing schizophrenia, given that concordance rates in identical twins is not 100%, environmental factors are also implicated (8). Epidemiologic findings on childhood development and academic performance have suggested that schizophrenia is a neurodevelopmental disorder. A retrospective study by Walker and colleagues examined home movies and identified subtle neuromotor dysfunction in children who later were diagnoses with schizophrenia (9,10). Findings from British and Scandanavian cohorts use retrospective examination of records find reductions in academic performance and social function in children and adolescents prior to their being diagnosed with schizophrenia. A number of other studies looking at premorbid functioning similarly suggest that development in childhood and adolescence is abnormal in persons who later are diagnosed with schizophrenia, and in particular schizophrenia with prominent negative symptoms (11, 12, 13).

Much ongoing work builds on these studies, shifting the focus to earlier points in development. In particular, the prenatal and early postnatal periods are of interest as critical time points for neurodevelopmental disruption. However, any study examining the relationship between prenatal factors and a disease that does not present symptomatically until late adolescence/early adulthood is logistically complicated and requires more financial and administrative resources than are typically available for work on a single study. Although unique circumstances and concerted collaborative efforts are permitting at least one prospective epidemiological study of prenatal factors to take place (14). Ecological studies form an important starting point from which more specific theories can be formulated and tested on an individual and molecular level.

Prenatal infection has been suggested as a risk factor for some time, e.g., even by Kraepelin and Bleuler (15). Recent investigations have looked at both specific infectious agents such as German measles (Rubella) and cytomegalovirus as well as generalized infection. While it has been noted that prenatal rubella exposure creates white matter hyperintensities, recent results from imaging studies and molecular examinations of DNA extracts from schizophrenics has not yielded conclusive results (16,17). The more general approach has resulted in an association between non-specific respiratory infection and schizophrenia spectrum disorder (SSD). Controlling for smoking, maternal age, and race, Brown and colleagues demonstrate a second semester relationship to SSD but neither a first, nor a second trimester association. Future studies will include serologic analyses for specific infectious agents (13)

In terms of general environment, residential and occupational settings have been examined as potentially schizophrenogenic environments. A relationship between residing in an urban setting and an increased incidence of schizophrenia was first demonstrated by Faris and Dunham,

and later by Eaton and colleagues (18). Recent work has confirmed that living in an urban setting increases the risk of developing schizophrenia, while seeking to clarify the mediating factors and also address the issue of temporal relationship, i.e., does psychosis emerge as a result of immediate exposure to urban settings or does urban upbringing and early life exposure act as a developmental disruptor? It appears that multiple features of urban life predispose both to increased risk and to worsened course of disease (19).

In addition to urban setting, another factor seems to impact on both incidence and on course of illness is diet. Studies in this area have investigated the relationship between prenatal folate deficiency, maternal body mass index, and other specific dietary components and indicators. One of the most illustrative examples of the effect of maternal diet is seen in the study of the Dutch Hunger Winter. During World War II, a Nazi blockade of Western Holland in 1944 disrupted food shipments into this industrial, urban area, resulting in a famine well-delineated in time and space in a society with well-documented health registries. The cohort of people exposed to the famine prenatally were assessed over many years. Work by Susser and colleagues demonstrated that the rate of schizophrenia was nearly doubled in that group conceived at the height of the famine when mothers were receiving an average energetic intake of less than 4,200 kilojoules per day. Studies examining CNS anomalies in the same cohort have shown an overall increase in white matter hyperintensities in those with first trimester exposure to famine. Imaging studies performed during adulthood on those with schizophrenia also shows an association with decreased cranial volume (20, 21, 22).

In another ecologic study, Christensen and Christensen, using data from a World Health Organization (WHO) international study comparing incidence and course of schizophrenia in eight different national centers, found that differences in dietary intake correlated with course and outcome but not incidence. Better course and outcome, including remission, was found in countries where unsaturated fatty acids from vegetables and fish comprised a major part of the diet, as compared to countries where saturated fatty acids from land animals and birds constituted a high percentage of fat intake (23).

4. CLINICAL OBSERVATIONS

Several intriguing clinical observations have not been pursued as aggressively as those related to dopamine and serotonin. Amongst these intriguing observations are the following:

1. Niacin Flush Reaction Abnormality: During treatment to lower serum cholesterol, niacin is sometimes administered. A side-effect to niacin treatment is the release of arachidonic acid (AA) and its conversion to prostaglandins. The resulting rise in vasodilating prostaglandins creates a strong flushing reaction. Horrobin noted over twenty years ago that the flush reaction was reduced in schizophrenics (24). Subsequent studies have produced mixed results in attempts to replicate this observation, as the response is affected by several other parameters, including gastrointestinal absorption. Topical administration of niacin has more consistently shown a decreased niacin flush reaction among schizophrenics when compared to normal controls result, with lower responses in 70% of neuroleptic-treated patients and in 90% in neuroleptic-naïve patients (25).

2. Increased Exhalation of Organic Compounds: Pulmonologists first noted alterations in the exhalation of volatile organic compounds (VOCs) in schizophrenics, leading to comparisons with both patients with other mental disorders and with normal controls. Phillips and colleagues (26) have identified 48 volatile organic compounds, including pentane and carbon disulfide, in air exhaled by schizophrenics. Using 11 of these compounds, a particular pattern has been identified with both high sensitivity (80%) and reasonable specificity (61.9%) in identifying schizophrenics. This pattern suggests increased membrane peroxidation and lipid turnover in schizophrenics (27).

5. ABNORMAL PHOSPHOLIPID METABOLISM IN SCHIZOPHRENIA: CONVERGING EVIDENCE

While epidemiological findings and clinical observations each have unique strengths and limitations, when findings from both sources converge, it increases the likelihood that the findings from each discipline are valid. Both support the hypothesis, articulated earlier by Horrobin and others, that for a subgroup of schizophrenics, an abnormality in phospholipid metabolism exists. Findings from the Dutch Hunger Winter suggest that early life nutrient deprivation increases the likelihood of developing schizophrenia. While no specific nutrient can be identified from the Dutch Hunger Winter findings, only total caloric intake, dietary lipid intake was definitely lowered from pre-famine levels. Analysis of WHO data by Christiansen and Christiansen suggests that a high ratio of saturated to unsaturated fatty acids in diet can affect the course and outcome of schizophrenia in a negative fashion. This results in greater severity of symptoms, and less likelihood of remission and recovery. In concert with these epidemiologic findings, clinical observation of decreased flushing when administered niacin suggests lower levels of intracellular essential fatty acids (EFA), while increased VOCs indicate increased phospholipid turnover in membranes.

6. PRELIMINARY CLINICAL TRIALS

Based on these and other findings suggesting that schizophrenia may involve a phospholipid deficiency, several investigators have conducted preliminary studies indicating that administration of omega-3 fatty acids (n-3) may offer benefit for some schizophrenics. Vaddadi and colleagues, hypothesizing that supplemental n-3 would improve dyskinetic movements, administered n-3 supplements to chronic schizophrenic patients (28). While improvements in tardive dyskinesia were statistically significant but not clinically meaningful, n-3 supplementation unexpectedly led to both statistically and clinically significant improvements in both memory and overall psychopathology.

Reports of erythrocyte membrane fatty acid composition by several groups have shown significant depletions in schizophrenics. In particular, deficiencies in AA, eicosopentanoic acid (EPA), docosohexanoic acid (DHA), and linoleic acid (LA) have been observed. Based on this observation, Peet *et al*. carried out a trial of EFA supplementation, administering 10 grams of MaxEPA, a dietary supplement containing a mixture of n-3 and omega-6 fatty acids and high in EPA content, to 20 chronic hospitalized schizophrenics receiving concurrent neuroleptic treatment. Significant improvements were observed in both symptoms severity as measured by the Positive and Negative Syndrome Scale (PANSS) and in tardive dyskinesia using the Abnormal Involuntary Movement Scale (AIMS) (29). These clinical improvements were associated with increases in omega-3 fatty acid content of erythrocyte membranes.

Puri *et al*. report the results of administering EPA to a neuroptic-naive schizophrenic patient (30). Significant improvements in positive and negative symptoms were observed. Additionally, increases in n-3 levels in erythrocyte membrane composition occurred, similar to those previously reported by Peet. Magnetic resonance spectroscopy revealed reduced neuronal membrane phospholipid turnover, while three-dimensional analysis of MRI images demonstrates reversal of cerebral atrophy, which had been observed prior to n-3 administration. In contrast to other studies and case reports, since this patient did not receive treatment with antipsychotics at any time, neither the deficiencies in EFA nor the beneficial effects seen can be ascribed to neuroleptics.

7. CONCLUSION

Epidemiologic findings and clinical observations suggest that at least a subgroup of schizophrenia involves an abnormality in phospholipid metabolism. Preliminary clinical trials suggest that administering n-3 may lead to improvement.

The convergence of epidemiology and clinical observation needs to guide research if we are to make progress in understanding the complex etiology and develop new treatments for schizophrenia and other major mental disorders. Epidemiologist, clinicians, and clinical researchers need to develop better ways of sharing information in a systematic, reliable, and mutually understandable manner.

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Send correspondence to: Dr Mark G. Opler Division of Env. Health Science, 60 Haven Ave. B-1, New York, NY 10032. Tel: 212-923-1164,Fax:212-305-9135, E-mail: mgo4@columbia.edu