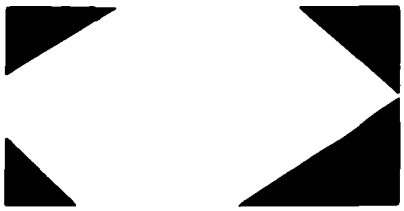
Genetic Hypothesis of Idiopathic Schizophrenia: Its Exorphin Connection

by F. Curtis Dohan

At Issue



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Abstract

This brief overview proposes a testable oligogenic model of the inheritance of susceptibility to idiopathic schizophrenia: "abnormal" genes at each of a few complementary loci. The model is based on my assumptions as to the likely genetic abnormalities at possibly four or five interacting loci that would permit exorphins, the opioid peptides from some food proteins, especially glutens and possibly caseins, to go from gut to brain and cause symptoms of schizophrenia. Exorphins may reach the brain cerebrospinal fluid (CSF) in harmful amounts because of their genetically increased, receptor-mediated transcellular passage across the gut epithelial barrier plus decreased catabolism by genetically defective enzymes. A schizophrenia-specific, genetically enhanced affinity for exorphins by opioid receptors influencing dopaminergic and other neurons would permit sustained dysfunction at low CSF exorphin concentrations. Tests of each postulated genetic abnormality are suggested. This model is supported by a variety of evidence, including a significant effect of gluten or its absence on relapsed schizophrenic patients, the high correlation of changes in first admission rates for schizophrenia with changes in grain consumption rates, and the rarity of cases of schizophrenia where grains and milk are rare.

Since the mode or modes of inheritance of idiopathic "true" schizophrenia remain undetermined, speculation may be fruitful. Among others, Vogel and Motulsky (1979, p. 187) have pointed out that "In the common diseases, particularly, a relatively small number of potentially identifiable major genes may contribute to the genetic etiology and explain most of the genetic variations." In section I, I propose a testable oligogenic model that is compatible with this concept and the clinical and genetic data on schizophrenia. It is based on my assumptions (from evidence presented in section II) about genetic abnormalities that would permit harmful amounts of neuropeptides from food proteins—particularly exorphins—to reach the brain and cause its dysfunction. Exorphins are families of many opioid peptides—some quite potent—produced by enzymatic action on grain glutens and milk caseins. The structures of gluten exorphins are still uncertain, but those for many exorphins from caseins are known. (For thorough reviews of the extensive literature on exorphins, see Paroli 1988; Zioudrou, in press.)

Idiopathic schizophrenia—by far the largest group—is the category to which all schizophrenic patients

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belong, provided they meet appropriate diagnostic criteria for schizophrenia and are not phenocopies (e.g., after viral encephalitis or associated with Huntington's disease). The belief that idiopathic schizophrenia is composed of genetic subgroups, each due to mutant genes at a different locus or loci and different etiologies, is not needed to explain its different manifestations, course, and outcome—phenotypic heterogeneity.

I. A Speculative Oligogenic/ Exorphin Model of Idiopathic Schizophrenia

This model is testable at many levels. It posits that the inherited susceptibility to idiopathic "true" schizophrenia is due to aberrant receptor and enzyme products of "abnormal" genes at each of a few complementary loci. According to a standard glossary of genetics, complementary genes are genes that by interaction produce an effect qualitatively distinct from the effects of any of them separately. Thus, interacting abnormal (i.e., less common) alleles increase the probability that the ingested opioid peptides from glutens—exorphins—will reach the brain cerebrospinal fluid (CSF) and, because of certain schizophrenia-specific abnormal opioid receptors, evoke symptoms of schizophrenia.

An Oligogenic Model. I posit that in the general population each of these (4–5?) complementary loci is polymorphic, that more than one abnormal allele exists for each locus, and that the quantitative effects of allele products of a given locus may differ. Hypothetically, the abnormal products of alleles for one locus might increase the activity of certain receptors on gut epithelial cells so that there is increased absorption of gluten exorphins/precursors by receptor-mediated endocytosis and transcellular passage into the blood and lymph. I also postulate that there are abnormal alleles at two or three loci coding for major enzymes catabolizing exorphins. Their defective function, plus daily, repeated gluten intake, would greatly increase the probability that absorbed gluten exorphins would reach the brain capillaries.

From the brain capillaries, exorphins could slowly enter the brain CSF via the circumventricular organs and diffusion of small hydrophobic gluten exorphins across the blood-brain barrier. However, this alone would not evoke idiopathic schizophrenia. I posit that genetic susceptibility to the disease absolutely depends on inheritance of one or two schizophrenia-specific abnormal alleles at a locus coding for an opioid receptor protein. These alleles, I hypothesize, cause brain dysfunction by enhancing the affinity for exorphins of certain opioid receptors that influence dopaminergic, and probably cholinergic, neurons. The same abnormality of the receptors may decrease their affinity for the endogenous opioids that normally modulate the functions of these neurons.

Heterogeneity. Under this model a spectrum of genotypes would be produced by (1) the quantitative differences in the effects of the inheritable abnormal alleles at each locus and (2) the inheritance of either one or two abnormal alleles at one or more of the few loci. An individual's inherited genotype would determine the upper limit (kinds and severity of the manifestations) of its phenotypic expression, often as the poorly delineated Kraepelinian subtypes. Within the upper limit, the symptoms and course would vary depending on exorphin types and concentrations in the brain CSF. These, in turn, are presumably strongly influenced by the types, frequency, and amounts of exorphin precursors consumed. However, some degree of variation in manifestations and course is undoubtedly due to contributing risk factors such as coping problems and previous brain damage.

What psychiatric symptoms, if any, result from the inheritance of abnormal genes at only some of these few loci? Clear-cut idiopathic schizophrenia will not occur if the genes determining the structure of certain brain opioid receptors are normal. If the gene products increasing the likelihood of exorphins reaching the brain (abnormal gut cell receptors and defective enzymes catabolizing exorphins) are only slightly abnormal but abnormal opioid receptor genes are present, symptoms compatible with the lower region of Kety's (1985) broad concept of the "schizophrenia spectrum" may occur. A brief, exceptionally large intake of gluten by such individuals might permit exorphins to reach the brain and produce a brief schizophrenic episode.

II. Evidence Pro and Con—and Ways of Testing the Model

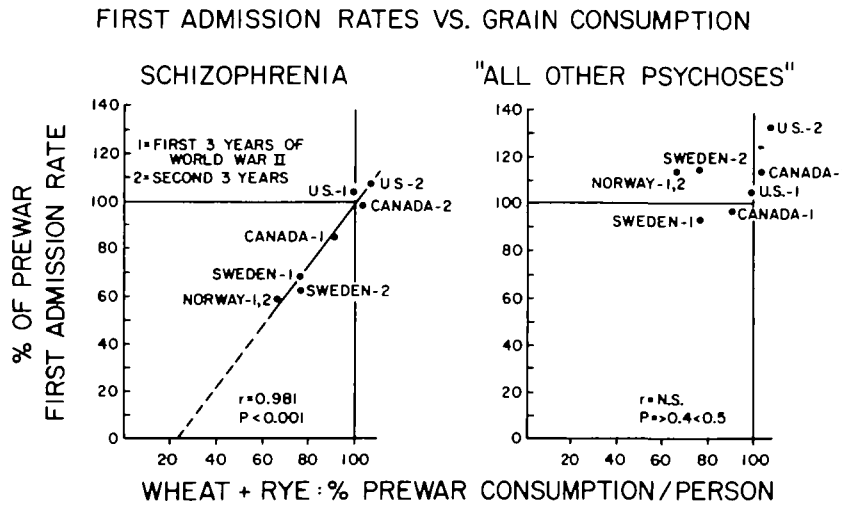
Epidemiologic Studies. In the 1960's, because of suggestive evidence that the gluten-evoked disorder, celiac disease, might share some but not all genes with schizophrenia, I examined the correlation

between differences from prewar values in grain consumption and first admissions "raw" data during World War II. These data, recalculated as percent of prewar rates (Dohan 1980), are shown in figure 1. Note the exceptionally high correlation ($r = .98$, $p < .001$) of wheat plus rye consumption with first admissions of women for schizophrenia. For men the correlation was lower ($r = .86$, $p = .02$). Because of the striking correlation, I and others have tested various aspects of the hypothesis that grain glutens are the major agents evoking idiopathic schizophrenia in individuals with its genotypes (see table 1).

For example, as expected from extension of the regression line, it was found (Dohan et al. 1984) that overtly psychotic cases of schizophrenia were extremely rare (two cases in over 65,000 adults) among three Pacific island populations that ate little or no grain and no cow's milk. When these populations consumed wheat, barley beer, and rice (but no milk), schizophrenia was common. Together, these epidemiologic data strongly suggest that grains are the major environmental agents evoking schizophrenia in individuals with its genotypes. Other tests of an etiological role of grain glutens are discussed below.

Clinical Trials. In the mid-1960's randomized clinical trials were conducted at a nearby Veterans Administration hospital (Dohan 1980). On admission to a diet-controlled locked ward from an open ward or the community, every patient was randomized to eat either a cereal-free, milk-free (CFMF), or a high cereal (HC) diet, but the patients ate the usual hospital diet after release to an open

Figure 1. Correlation (.98) between rates of wheat plus rye consumption with first admission rates of women with schizophrenia; first admission rates for "all other psychoses" were not correlated



Values for each of the countries during World War II are plotted as the % of prewar baseline value This minimizes the confounding effects of intercountry differences in methods of estimating grain consumption and the differences in diagnostic criteria, definitions of "first admissions," and nosocomial factors (Dohan 1980)

Table 1. Major evidence that peptides from grain glutens evoke idiopathic schizophrenia in those with its genotypes

1. In the 1960's many observations suggested schizophrenia and celiac disease, gluten enteropathy, share some but not all genes. Therefore, the role of gluten in schizophrenia was examined.

2. Epidemiologic studies demonstrated a strong, dose-dependent relationship between grain intake and the occurrence of schizophrenia—no data on cow's milk.

3. Clinical trials and case reports show that gluten is toxic for acute and relapsed schizophrenic patients, but only occasional long-term chronic patients respond to gluten or its absence.

4. Because of the evidence above, peptides with potent opioid activity were sought and found by National Institutes of Health investigators in enzymatic digests of gluten, its gliadin subfraction, and α-casein from milk. These opioid peptides were named exorphins.

5. Urinary excretion of small peptides by individuals with schizophrenia is greatly increased. Some are apparently from gluten. Some peptides are neuroactive, including opioid-like effects.

6. A specific gliadin peptide fraction, which in large doses is psychoactive in individuals with celiac disease, produced stereotyped behaviors and limbic seizures in rats hours after intracranial injection.

ward. Neuroleptics and other customary treatments were given. In a study of 102 such patients, we found that the CFMF diet hastened release to an open ward (exact p = .009). Addition of wheat gluten to the CFMF diet without the staff or patients knowing about it abolished this effect. Diet did not affect the heterogeneous nonschizophrenic group. In this and a subsequent study, we examined the effect of diet on 115 relapsed or acute schizophrenic patients admitted to the locked ward directly from the community. We found that patients randomized to the ward CFMF diet were discharged from the hospital twice as fast as the HC group (exact p = .009).

Singh and Kay (1976) used a CFMF diet during three periods of 4 weeks each to study 14 schizophrenic patients; 13 were being given neuroleptics. As a group they improved in the first CFMF period, were significantly worse during the second period when gluten was added to the CFMF diet, and again improved when gluten was excluded in the third period. In addition, an occasional severe neuroleptic-resistant chronic schizophrenic patient may in a month or so be made worse by gluten and better by its absence. Rice et al. (1978) and Vlissides et al. (1986) reported that 2 out of 16 and 2 out of 17, respectively, of such schizophrenic patients clearly responded to these changes.

In contrast, there are three negative trials. King (1985) concluded that the negative studies had, because of small samples, a probability of < .3 of detecting a moderate effect compared with .52 and .75 for the positive studies of Singh and Kay (1976) and the hospital discharge study noted above (Dohan 1980). A randomized, double-blind clinical trial of only 10 days (Storms et al. 1982) produced no worsening of 13 schizophrenic patients given a CFMF plus gluten diet compared to 13 on a CFMF plus peanut flour diet. Osborne and colleagues (1982) noted no decrease in severity of four chronic schizophrenic patients given a gluten-free diet for 36 weeks. Potkin and colleagues (1981) reported that eight chronic schizophrenic patients on a CFMF diet were not made worse by gluten for 5 weeks. Five of the eight patients had enlarged ventricles (L. Bigelow, personal communication) suggesting dead, therefore unresponsive, neurons. Might excessive stimulation by exorphins of dopamine (DA) neurons during the stage of positive symptoms, Crow's Type I (Crow et al. 1982), sporadically kill DA neurons and gradually produce the stage of predominately negative symptoms, Crow's Type II?

Celiac Disease as a Guide. Graff and Handford (1961) reported that 4 of 37 adult schizophrenic patients had a history of celiac disease in childhood—possibly 50 to 100 times the rate that would be expected by chance. As emphasized by me (Dohan 1983), this neglected finding was supported in the 1960's by letters to me from four more investigators of schizophrenia (who found about 1.9 recognized active or inactive celiacs/100 schizophrenic patients), and four investigators of celiac disease (who noted 6 schizophrenic patients among 115 gut-biopsy proven celiac patients in the Philadelphia, Baltimore, and New York regions). Both examples are greater than 10 times chance expectancy.

Many other associations suggest celiac and idiopathic schizophrenic individuals share some but not all genes. For example, before World War II—when neuroleptics were unknown and grain consumption in Europe and the United States was much higher than recently—schizophrenic patients exhibited an increased frequency of clinical (e.g., unexplained marked fluctuations in body weight and gut symptoms), biochemical (e.g., poor iron absorption) and post-mortem abnormalities like those subsequently discovered in celiac patients. Because of the great decrease in grain consumption and the effects of neuroleptics on the gut (e.g., inhibition of the increased gut permeability produced by cholera toxin), it is unlikely that such changes would be found now in neuroleptic-treated schizophrenic patients.

The speculative oligogenic model for idiopathic schizophrenia posits that the abnormal alleles coding for enhanced gut cell receptor activity for gluten peptides and the alleles at the two or three loci, which code for defective exorphin-catabolizing enzymes, are the same in celiac and schizophrenic patients. However, inheritance of susceptibility to celiac disease also requires genes at another locus. The abnormal alleles at this locus in celiac patients code for increased immunologic response to gluten plus some other antigens and is in linkage disequilibrium with a few HLA loci (e.g., B8 and DW3). These occur in most celiac patients, but are not increased in schizophrenic patients above the much lower frequency in the general population.

Genetic Test. This model's initial hypothesis—some abnormal genes but not all are common to schizophrenia and celiac disease—should be tested by controlled genetic/epidemiologic studies of the past and present occurrence of celiac disease

in schizophrenic probands and their first-degree relatives and vice versa.

Biological Tests. Evidence of enhanced activity of a receptor for gluten peptides on gut epithelial cells should be sought in both schizophrenia and celiac disease. For example, Bruce et al. (1985) have proposed that the greatly increased activity of transglutaminase (EC 2.3.2.13) found in gut biopsies of active and remitted celiac patients might increase the binding of the glutamine-rich gluten peptides. This might increase their receptor-mediated endocytosis and transcellular passage into blood and lymph of jejunal villi.

Defective exorphin-catabolizing enzymes, due to alleles at two or three loci, are posited in both schizophrenia and celiac disease. Endopeptidase-24.11—"enkephalinase"—(Kenny 1986) should be measured in both diseases. Enkephalinase, which catabolizes a variety of peptides, is abundant in kidney, jejunum, and lymph nodes. Importantly, it is clearly present in the choroid plexus, substantia nigra, striatum, amygdala, and hippocampus (Pollard et al. 1987). Pyroglutamyl peptidase in blood platelets of schizophrenic patients is decreased (K. Reichelt, personal communication). This needs investigation in both diseases. Since the potent proline-rich exorphins from β-casein may be pathogenic (see below), the enzymes catabolizing them deserve attention.

Obtaining evidence of abnormal alleles at the posited locus affecting brain opioid receptors will be more arduous (e.g., requiring many suitable post-mortem brains). After the structures of potent gluten exorphins are known, their relative affinity for opioid receptors may be studied by positron emission tomography (PET), considering such problems as possible slow passage of exorphins into the CSF.

Less specifically, methods might be developed that measure the concentration of gluten peptides in body fluids. Reichelt et al. (1985) reported that small peptides—some possibly from gluten—are greatly increased in the urine of individuals with schizophrenia and untreated celiac disease. Measurements before and after an oral dose of gluten might be developed into a test for those with the genotypes for the gluten-evoked disorders. Oral administration of isotope-labeled gluten peptides would be particularly valuable.

A gluten tolerance test could be combined with measurement of the urinary excretion of *N*-terminal pyroglutamyl peptides, since these were increased in a celiac patient given gluten and in schizophrenic patients (Reichelt et al. 1985). Measurement of exorphins in CSF and blood by radioreceptor and radioimmunoassay techniques would provide important information. For example, β-casomorphin-like peptides, probably formed in the lactating breasts, were increased in blood and CSF of women with postpartum psychosis (Terenius et al. 1987). This suggests that these peptides from the breasts entered the brain and adversely affected its function.

Many other tests are possible; for example, if ethically acceptable, would high-gluten diets evoke the disease in monozygotic twins discordant for schizophrenia? Does naloxone inhibit the demonstrated gluten peptide effect on migration of schizophrenic patients' leukocytes in agarose as it does with celiac patients' leukocytes? Do the electroencephalographic (EEG) abnormalities noted in many schizophrenic patients disappear on a gluten-free diet as do the EEG changes of celiac patients?

Conclusion

Abnormal alleles at each of a few complementary loci may account for the genetic variations of idiopathic schizophrenia. Together, these mutant genes increase the probability that opioid peptides from ingested glutens, exorphins, will cause brain dysfunction. From the practical viewpoint, careful long-term studies are needed to test the effect of diet in large numbers of early schizophrenic patients and to test the various subhypotheses presented above. I would be glad to discuss tests of the oligogenic/exorphin model with interested investigators.

References

Bruce, S.E.; Bjarnason, I.; and Peters, T.J. Human jejunal transglutaminase: Demonstration of activity, enzyme kinetics and substrate specificity with special relation to gliadin and celiac disease. *Clinical Science*, 68:573–579, 1985.

Crow, T.J.; Cross, A.J.; Johnstone, E.C.; and Owen, F. Two syndromes in schizophrenia and their pathogenesis. In: Henn, F.A., and Nasrallah, H.A., eds. *Schizophrenia as a Brain Disease.* New York: Oxford University Press, 1982. pp. 196–234.

Dohan, F.C. Hypothesis: Genes and neuroactive peptides from food as cause of schizophrenia. In: Costa, E., and Trabucchi, M., eds. *Advances in Biochemical Psychopharmacology.* Vol. 22. New York: Raven Press, 1980. pp. 535–548.

Dohan, F.C. More on celiac disease as a model for schizophrenia. *Biological Psychiatry*, 18:561–564, 1983.

Dohan, F.C.; Harper, E.H.; Clark, M.H.; Rodrigue, R.B.; and Zigas, V. Is schizophrenia rare if grain is rare? *Biological Psychiatry*, 19:385–399, 1984.

Graff, H., and Handford, A. Celiac syndrome in the case histories of five schizophrenics. *Psychiatric Quarterly*, 35:306–313, 1961.

Kenny, A.J. Regulatory peptide metabolism at cell surfaces: The key role of endopeptidase-24.11. *Biomedica Biochimica Acta* (Berlin), 45:1503–1513, 1986.

Kety, S.S. The concept of schizophrenia. In: Alpert, M., ed. *Controversies in Schizophrenia: Changes and Constancies*. New York: The Guilford Press, 1985. pp. 3–11.

King, D.S. Statistical power of the controlled research on wheat gluten and schizophrenia. *Biological Psychiatry*, 20:785–787, 1985.

Osborne, M.; Crayton, J.W.; Javaid, J.; and Davis, J.M. Lack of effect of a gluten-free diet on neuroleptic blood levels in schizophrenic patients. *Biological Psychiatry*, 17:627–629, 1982.

Paroli, E. Opioid peptides from food. In: Bourne, G.H., ed. *World Review of Nutrition and Dietetics*. Vol. 55. Basel. S. Karger AG, 1988. pp. 58–97.

Pollard, H.; Llorens-Cortes, C.; Couraud, J.-Y.; Ronco, P.; Verroust, P.; and Schwartz, J.-C. Enkephalinase (EC 3.4.24.11) is highly localized to a striatonigral pathway in rat brain. *Neuroscience Letters*, 77:267–271, 1987.

Potkin, S.G.; Weinberger, D.; Kleinman, J.; Nasrallah, H.; Luchins, D., Bigelow, L.; Linnoila, M.; Fischer, S.H.; Bjornsson, T.D., Carman, J.; Gillin, J.C.; and Wyatt, R.J. Wheat gluten challenge in schizophrenic patients. *American Journal of Psychiatry*, 138:1208–1211, 1981.

Reichelt, K.L.; Edminson, P.D.; and Toft, K.G. Urinary peptides in schizophrenia and depression. *Stress Medicine*, 1:169–181, 1985.

Rice, J.R.; Ham, C.H., and Gore, W.E. Another look at gluten in schizophrenia. *American Journal of Psychiatry*, 135:1417–1418, 1978.

Singh, M.M., and Kay, S.R. Wheat gluten as a pathogenic factor in schizophrenia. *Science*, 191:401–402, 1976.

Storms, L.H.; Clopton, J.M.; and Wright, C. Effects of gluten on schizophrenics. *Archives of General Psychiatry*, 39:323–327, 1982.

Terenius, L.; Lyrenas, S.; Lutsh, H.; Lindstrom, L.; Nyberg, F.; and Lindberg, B. Opioid peptides at term pregnancy in the early puerperium and in postpartum psychosis. In: Nerozzi, D.; Goodwin, F.K.; and Costa, E., eds. *Hypothalamic Dysfunction in Neuropsychiatric Disorders*. New York: Raven Press, 1987. pp. 201–209.

Vlissides, D.N.; Venulet, A., and Jenner, F.A. A double-blind gluten-free/gluten-load controlled trial in a secure ward population. *British Journal of Psychiatry*, 148:447–452, 1986.

Vogel, E., and Motulsky, A.G. *Human Genetics*. New York: Springer-Verlag, 1979.

Zioudrou, C. Food derived psychoactive peptides. In: Rippere, V., ed. *Diet and Mental Disorders*. London: Croom Helm, in press.

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Erratum

In the article by Craig N. Karson et al. entitled "Computerized EEG in Schizophrenia" (*Schizophrenia Bulletin*, 14:193–197, 1988) figures 1 and 2 were transposed. Figure 1 refers to the color print at the bottom of the page, and figure 2 appears on the top of the page.