

An Hypothesis for a Mechanism for the Pathogenesis of Psychomimetic Symptoms in Gluten/Gliadin Sensitive Individuals

Carl F. Washburn, Jr., N.M.D.¹ and Ronald G. Reichert, N.D.²

Abstract

A review of the literature suggests a possible correlation between gluten/gliadin ingestion and the pathogenesis of schizophrenic-like symptoms in certain individuals. Hydrolysis of the gliadin fraction of wheat protein, in the presence of pepsin, produces peptides resembling the endogenous opiate peptides (endorphins). These opiate peptides have been demonstrated to enter the bloodstream from the digestive tract and cross the blood brain barrier with sufficient retention of structure to possess an opioid-like activity. The known psychomimetic activity of opioid substances suggest a possible link between gluten/gliadin ingestion and psychological dysfunction due to this biochemical mechanism.

The relationship between gluten/gliadin sensitivity and the pathogenesis of the psychological dysfunction of schizophrenia remains a subject of controversy in spite of a growing body of well controlled research. A significant subset of diagnosed schizophrenics have been demonstrated to respond in a positive manner to the elimination of wheat, cereal grains or both from the diet.^{5 6 14 21 23} The major stumbling block to acceptance of the gluten/gliadin response appears to be the lack of a clear mechanism to explain the basis of the manifestation of psychological dysfunction in some but not all individuals following ingestion of this protein substance.^{7 15 16 20 14} We are in complete agreement with Cott, Pauling, Williams, and Hoffer in the belief that a constellation of biochemical disorders are capable of producing psychological dysfunction with

similar symptoms.^{4 12 14 27} That is to say, schizophrenia is not a single disease entity, but rather a complex manifestation of biochemical disorders producing perceptual and psychological distortion by interference with normal biological functions. The now commonly recognized psychological symptoms of Korsakoff's psychosis, pellegra, and heavy metal poisoning by lead and mercury are examples of this phenomenon. From this perspective, we would like to suggest a neurobiological mechanism which may mediate the psychological dysfunction seen in gluten/ gliadin sensitive individuals.

There is no single mechanism universally accepted for the pathogenesis of schizophrenia. Currently, the most widely accepted neurobiological mechanism is the "dopamine hypothesis". Over activity of the dopaminergic pathway of the meso-limbic-frontal corticle mantle is believed to result in the perceptual thought disorder which characterizes schizophrenia.^{2 9 13} The support for this hypothesis comes from the data demonstrating the dopaminergic antagonism of the antipsychotic drugs.^{9 13} Dopamine is not the only substance in the biochemical environment of the brain capable of inducing psychomimetic symptoms in susceptible individuals. Neither is it the only substance whose psychological effect can be reversed by a pharmacological antagonist.

The endogenous opiate peptides (endorphins) have yet to be fully illucidated. At this time 10-15 substances of 5-31 amino acid sequence are know to exist.²² These substances are present throughout the brain, with substantial concentration of receptor sites in areas of the brain associated with the limbic system.²² This area of the brain is known to be involved with the expression of emotions, memory, and learning.

1. 2734 Audry Ave., Waukegan, Illinois, U.S.A. 60087.

2. Suite 7, 1742 Marine Dr., West Vancouver, B.C., Canada V7V 1J3.

A pathway between the dience-phalon and the frontal cortex has been postulated, and the high density of opioid binding sites in the thalamus and hypothalamus tend to support this hypothesis.²⁵ Dysfunction of the limbic and frontal cortex areas of the brain are the basis for the perceptual distortion identified in the dopamine hypothesis. Since these regions of the brain have already been identified as being capable of inducing psychomimetic symptoms, it is not unreasonable to presume that any biochemical substance interacting with these areas may be capable of causing dysfunction if over-stimulation occurs. It has been reported that endorphins are capable of inducing rage and catatonia in animal models.²² Based upon these models of the known effects of endorphins, altered levels of endorphins or endorphin receptors have been suggested to be responsible for some psychotic symptoms in humans as well.^{12 18 22}

The well known ability of exogenous opioid substances to induce euphoria/dys-phoria and analgesia was the basis for the original research into the existence of the endorphins.¹⁰ The fact that certain classes of exogenous opioids are capable of crossing the blood brain barrier has been well documented.^{8 25} Once having made the transition from the digestive tract and blood stream to the biochemical environment of the brain, interaction with the various classes of receptor results in the observed pharmaceutical activity. Of the various types of receptor currently identified, sigma receptors appear to be related to the ability of exogenous opioids to produce psychological symptoms such as euphoria/dysphoria and hallucination.²⁵ The interaction between sigma receptor and opioid molecule producing euphoria has been suggested to be the principle CNS effect of exogenous opioids in man.⁸ However, the overall effects on perceptual functioning are not known. Analgesia induced by opioid substances is said to resemble a "frontal lobotomy" where pain is known to exist, but no longer has a perceptual meaning to the sufferer.²⁵ At least one author has stated that the overall stimulatory effect on the brain is not unlike the "wild excitement" induced in feline species by administration of codeine.⁸ The

documented psychological activity of mixed agonist/antagonist opioids tends to support this "wild excitement" effect. Pentazocine is well documented to have psychomimetic effect on certain individuals. The induced hallucinations, anxiety and night terrors are not unlike the marked perceptual distortion of self and world seen in early schizophrenia.^{2 25} We believe this exogenous opioid effect may be the mechanism producing the psychological dysfunction seen in gluten/gliadin sensitive individuals.

A review of the literature demonstrates that pepsin hydrolysates of wheat gluten/ gliadin possess a structure similar to the endorphins.^{17 28} Entry of large molecules derived from digestion of gluten/gliadin into the general circulation and across the blood brain barrier has been demonstrated by both antibody titer and radioactive labeling of molecules.^{1 11 16 28 29} To presume that if a substance has maintained enough structural integrity to induce an antibody response, it would also be capable of inducing a pharmacological response is in keeping with current pharmacodynamic theory. We feel justified in this presumption by the fact that of the currently identified endorphins, met-endorphin and leu-endorphin consist of only 5 amino acids in sequence.²² Any substance which possesses an amino acid sequence similar to endorphins will have pharmacologic effect. The question to be answered is only how strong the effect will be. The comparison between endorphins and opioid analgesics shows the endorphins to be up to 200 times more potent.^{22 25}

There are a number of plausible explanations for shifting the equilibrium of exogenous opiate peptide activity toward psychomimetic effect in some individuals. The rationale for the observed variation in response to exogenous opiate peptides derived from gluten/gliadin may be a matter of relative concentration, concentration of receptor sites, or interaction between variant endorphin and exogenous opiate peptide. One explanation which seems very reasonable is a genetic variation in the multiple alleles coding for enzyme activity, or structural protein. The fact that the substitution of a single amino acid in a peptide chain of an endogenous structural

protein, or variant enzyme activity can have a profound effect on the health of the individual is well documented. It is quite possible for the disease effects to remain masked until an exogenous challenge forces it to surface. PKU, G6PD, sickle cell disease, and intolerance of sulfa drugs are obvious examples.¹⁹ If we accept the report of Dr. Roger Williams on the observed variation of enzymatic activity within apparently healthy populations, the likelihood that a metabolic mechanism such as this is involved in gluten/gliadin sensitivity is readily considered.²⁷

If this exogenous opiate/endorphin mechanism is correct, reversing the effect with an opioid antagonist should be possible. This appears to be the case. As with the effects of the mixed agonist/antagonist drugs, hallucination in some schizophrenic humans, and psychomimetic behaviour in animal models, have been shown to respond favourably to Nalaxone HCl.^{22 26} We feel that the likelihood that a psychotic individual will respond to the currently utilized antipsychotic drugs may also involve this antagonistic mechanism. A conversation with Dr. Abram Hoffer, and a review of the known interaction of some classes of antipsychotic drugs with exogenous opiates suggest two possible interactions. It is possible that part of the effect of antipsychotic drugs may be due to metabolite interference with phenylalanine metabolic pathways in general, as well as dopamine receptors.¹² Phenylalanine is believed to be able to block the activity of the enkephalinase enzymes and prolong the effect of endorphins, this is suggested to be the basis of the pain relieving action of D/L phenylalanine.³ If the currently utilized antipsychotic drugs block the effect of phenylalanine, it may result in an increase in the activity of the enkephalinase enzyme system. This would result in more rapid breakdown of endorphins and endorphin similar exogenous substances. This would be in keeping with our belief that endogenous/exogenous opiate peptide molecule receptor interaction is responsible for some cases of schizophrenia. The ability of Chlorpromazine to control morphine induced mania in cats, and apomorphine's ability to override the sedative effect induced by Chlorpromazine definitely suggest an interaction that is not solely mediated

by affinity for dopamine receptors.⁸

Testing this hypothesis solely by elimination of gluten/gliadin sources from the diet would produce the same sort of results currently seen in the literature. There is, at this time, no conclusive method to identify those individuals who are most likely to respond to this intervention. We suggest that the use of low dosage of Nalaxone HO may provide a method of both reversing psychomimetic effect and identification of individuals who are likely to respond to this intervention. As noted earlier, Nalaxone HCl has been demonstrated to be effective in both human and animal models for reversal of psychomimetic symptoms. Product information provided by Du Pont Pharmaceuticals, as printed in the 43rd edition of the Physician's Desk Reference, suggest that the potential for adverse effect from low dosage of Nalaxone HCl (trade name NARCAN) is very low.³⁰ The plasma half life of 30-81 minutes should provide enough time for observation of improvement of psychological functioning without the need for repeated administration. We feel that the evidence in support of the neurobiological mechanism for induction of psychomimetic symptoms due to gluten/gliadin ingestion is sufficient to warrant this intervention as a method of testing this hypothesis.

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