Prostaglandin Deficiency and Endorphin Excess in Schizophrenia:

The Case for Treatment with Penicillin, Zinc, and Evening Primrose Oil

David F. Horrobin, B.M., M.A., D.Phil. [1]

Introduction

The dominant orthodox biological concept of schizophrenia is that it is somehow related to an excess of dopamine activity in critical areas of the brain. The outstanding pieces of evidence in favor of this concept are that all the commonly used anti-schizophrenic drugs are blockers of dopamine receptors and that two groups have now reported that certain regions of the brain in schizophrenics exhibit supersensitive dopamine receptors (Owen et al., 1978).

This dopamine hypothesis has been challenged by the Orthomolecular concept that schizophrenia may be related to problems in vitamin and mineral metabolism and more recently by the idea that schizophrenia may be related either to excess of one of the group of natural opiates or to a deficiency of synthesis of prostaglandins of the 1 series. Within the last six months it has become apparent that the dopamine, Orthomolecular, endorphin, and prostaglandin approaches may all be partly correct. To use a familiar analogy, schizophrenia is an elephant and the enthusiasts for each concept have been blind men looking at only one part of the beast. It is now possible to propose a unified concept of schizophrenia which encompasses all four approaches and which leads to strikingly novel approaches to treatment.

The Orthomolecular approach is well understood by readers of this Journal, and the dopamine concept has been so well aired that most people interested in biological psychiatry are conversant with it. The endorphin and prostaglandin approaches are less well known and will therefore be briefly described.

Clinical Research Institute, 110 Pine Avenue West, Montreal H2W1R7, Canada.

Schizophrenia as a deficiency of 1 series prostaglandins

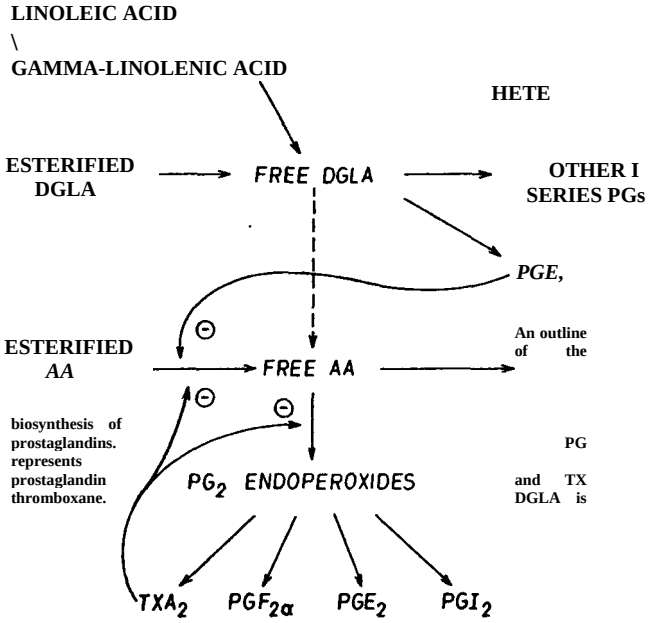
The prostaglandins are a family of unstable acidic lipids, originally isolated from prostatic fluid but now known to be present in every cell in the body (Horrobin, 1978c). They are synthesized from the vitamin-like essential fatty acids (EFAs), and recent evidence suggests that the primary if not the only function of the EFAs is to act as precursors for prostaglandins. The commonest naturally occurring EFA is linoleic acid which is found abundantly ir> vegetable oils. It rs converted to gamma-linolenic acid (GLA), to dihomo-gamma linolenic acid (DGLA), and to arachidonic acid. GLA and DGLA are present in the diet in only very small quantities, but there are substantial amounts of arachidonic acid in such foods as meat, seaweed, and some dairy products. The conversion of linoleic acid to GLA seems to be a reaction which is susceptible to inhibition by other fats in the diet. It also tends to fail in diabetics and in the elderly.

There are two main natural series of PCs. The 1 series is formed from DGLA and has one double bond in the side chains. The 2 series is formed from arachidonic acid and has two double bonds in the side chains. Each series contains a number of different compounds and an outline of the metabolic pathway is shown in Figure 1. There is recent evidence that PGE1 may regulate the synthesis of 2 series PCs, a deficiency of PGE1 leading to excess formation of 2 series PGs. Thromboxane (TX) A2 may also exert a negative feedback control over formation of the 2 series.

My interest in the PGs began with the observation that virtually all effective antischizophrenic drugs are potent stimulators of secretion of prolactin from the anterior pituitary (Langer et al., 1977). This occurs because prolactin secretion is inhibited by dopamine and hence increased by dopamine blockade. The prolactin secretion is thought to be merely a side effect of the therapy. However, the evidence is consistent with the possibility that prolactin itself may have a therapeutic action. I therefore studied the effects of prolactin on an excitable tissue, vascular smooth muscle.

Eventually we discovered that the effects of prolactin in this tissue could be accounted for by its specific stimulation of the synthesis of PGs of the 1 series without any effect on 2 series PGs (Manku et al., 1979). If prolactin is therapeutic and if it works by enhancing synthesis of 1 series PGs, then there should be a deficiency of 1 series PGs in schizophrenia.

FIGURE 1



dihomogammalinolenic acid and AA is arachidonic acid. HETE is a product which can be formed from arachidonic acid by a lipoxygenase enzyme.

To my considerable surprise I soon found that there was direct evidence for such a deficiency in the platelets of severe paranoid schizophrenics off drug therapy. Of 20 such patients, all failed to increase the formation of PGE1 from DGLA in response to ADP. In contrast eight normal, 10 depressed, and eight manic individuals all increased PGE1 synthesis four to fivefold. This difference between schizophrenics and nonschizophrenics was significant at the p<10"7 level and was particularly striking because the gap between the lowest nonschizophrenic and the highest

schizophrenic value for PGE1 synthesis was more than eight times the range within either group, because there were no exceptions, and because the observation was completely unexpected by the authors (Abdullah and Hamadah, 1975). In contrast to synthesis of 1 series PCs, synthesis of 2 series PGs is probably normal or enhanced in schizophrenics since their platelets have normal or increased aggregability which can be reduced in the usual way by aspirin which blocks formation of all prostaglandins (Boullin and Orr, 1976).

The prolactin effect and the platelet studies therefore point to a failure of normal formation of 1 series PGs coupled with normal or perhaps excess formation of 2 series PGs (because of removal of PGE1 control) in schizophrenics. There is a large amount of indirect evidence pointing to a prostaglandin defect in schizophrenia, and this has recently been reviewed in detail (Horrobin, 1977; Horrobin et al. 1978). The most striking points are as follows:

1. The almost complete absence of rheumatoid arthritis in schizophrenics. In rheumatoid arthritis there is now good evidence of an overproduction of PGs.

2. The resistance of schizophrenics to pain and to histamine. PGs play an important role in pain.

3. The often recorded improvement in schizophrenia during febrile illnesses. Brain PEG1 levels rise during fever.

There is therefore a large amount of evidence pointing to the idea that there is an abnormality of PG synthesis in schizophrenia, probably a deficiency of formation of 1 series PGs coupled with normal or excess synthesis of 2 series PGs.

Endorphins, enkephalins, and exorphins

The endorphins and enkephalins are a group of recently described substances which have the remarkable property of being able to activate the receptors to which morphine and other narcotics become attached (Kosterlitz and Hughes, 1977; Guillemin, 1977). It seems that the narcotics work because they activate receptors normally occupied by this new class of peptides. The endorphins and enkephalins
were originally found in brain tissue and as fragments of the amino acid sequence of beta lipotrophic hormone, but it seems increasingly probable that they are widely distributed in the body.

The idea that the endorphins might play a role in schizophrenia was first proposed when it was found that their injection into animals produced a motor state superficially similar to human catatonia. This was followed by the disputed observation that schizophrenic hallucinations might be reversed by the narcotic antagonist naloxone. Very recently it has been found that blood and cerebrospinal fluid from schizophrenics may contain either an abnormal endorphin or excess amounts of a normal one, and that such endorphins may be removed from the blood during hemodialysis of schizophrenics (Terenius, 1978). This provides strongly suggestive evidence that an endorphin-like agent may be responsible for the schizophrenic state.

Very recently new excitement has been generated by the discovery by Klee and his group (Zioudrou et al., 1979) of substances which they have christened the exorphins. Like the endorphins these can activate opiate receptors and produce behavioral changes. The exorphins are, however, peptides produced by digestion in the gut of proteins, particularly those from wheat products. The group have suggested that the exorphins are the substances involved in those schizophrenics who respond to removal of wheat from the diet.

Four biological approaches: resolution of a controversy

It is now possible to link logically the four approaches to schizophrenia. Three observations in addition to those just outlined are required to make the connections.

1. Chronic treatment with narcotic drugs leads to dopamine supersensitivity in the brain (Lai, 1975). It seems probable that chronic overstimulation of opiate receptors by an endorphin-like agent will have the same effect.

2. p-endorphin has actions consistent with specific inhibition of formation of 1 series PCs without apparent effect on 2 series PCs (Horrobin, 1978b and c).

3. The formation of PGs from linoleic acid involves a series of additions of carbon atoms and oxidation-reduction reactions in which several vitamins are intimately involved. The details are not yet clearly defined, but it is obvious that abnormalities of vitamin intake or metabolism could lead to defective PC synthesis. Zinc in physiological concentrations seems specifically to activate formation of 1 series but not 2 series PGs (Manku et al., 1979).

I therefore propose that the schizophrenias are a group of diseases in which PG synthesis is abnormal and in particular in which the formation of 1 series prostaglandins is defective. I suggest that there are at least three main groups of schizophrenialike diseases, each probably with several subgroups.

A. Those related to formation of an ab normal endorphin-like agent, or of a normal one in excess.

B. Those related to production from the food of an exorphin as a result of digestion, usually of wheat products.

C. Those related to failures of vitamin and mineral intake or metabolism leading to defective PG formation. Zinc which may be a required cofactor for the formation of 1 series PGs may be of particular importance.

There are of course other possibilities, such as inborn errors of prostaglandin formation.

Exorphins and endorphins will lead to both a deficiency of 1 series PGs and to dopamine supersensitivity. Defects in minerals and vitamin metabolism may also lead to PG deficiencies. The current competing theories can be seen to be different aspects of the same schizophrenic elephant (Horrobin, 1978a).

Rational Therapy

If a schizophrenic syndrome is related to a mineral or vitamin deficiency, then rational therapy obviously consists in correcting that deficiency, an approach well documented in this Journal. I therefore propose to concentrate on rational therapy of the endorphin/exorphin schizophrenias.

First it is important to understand why the existing neuroleptics work since they are undoubtedly effective in many schizophrenics. They attack simultaneously two targets, the dopamine supersensitivity and the deficiency of 1 series PGs. The dopamine supersensitivity is opposed by blockade of dopamine receptors. The PG1 deficiency is opposed by stimulation of prolactin secretion which will specifically enhance formation of 1 series PGs. Which of the two is more important in reversing the schizophrenic state is uncertain. However there is good evidence that PGs may regulate receptor function (Horrobin, 1978c) and that increasing PG1 synthesis without dopamine blockade may improve schizophrenics (see below). My prejudice therefore is that the dopamine supersensitivity may be a consequence of the PG1 deficiency and that reversing the latter is thus the more important.

If the endorphins/exorphins are important in schizophrenia, then there are three basic approaches which may prove successful in therapy. These are to prevent their formation, to increase their removal, and to oppose their actions.

Prevention of formation is already being unwittingly practiced in the case of the exorphins. A gluten-free diet may be acting in precisely this way. As yet we know almost nothing about the regulation of endorphin formation, but when this information becomes available it is to be anticipated that new potentiat strategies for control will become apparent.

Enhancement of removal is also probably already being practiced in the form of hemodialysis. Seely has pointed out that for substances like endorphins controlled sweating may be very effective and this offers a potentially much less dangerous approach (Seely, 1978). It is interesting to note that Turkish baths were in vogue for the treatment of insanity a hundred years ago (Walford, 1877). Not only would sweating

remove endorphins and exorphins, it would also stimulate prolactin secretion and PG1 formation since a sauna is the most potent known natural method of stimulating prolactin secretion.

Antagonism of the endorphin/exorphin action might be achieved by direct stimulation of synthesis of the 1 series PGs if a deficiency of these PGs is indeed important in the production of the features of schizophrenia. Again this is already being unwittingly carried out by the prolactin whose secretion is stimulated by neuroleptics and by the zinc which is advocated by some Orthomolecular therapists.

I believe that the last of these approaches may, at least in the short term, prove most fruitful. The principles of opposing the opiate action are clear.

1. The provision of adequate amounts of PG precursors.
2. The provision of adequate amounts of all the cofactors required for PG synthesis.
3. The use of a pharmacological agent which will directly reverse the opiate effect on synthesis of 1 series PGs.

About 18 months ago we began to screen a very large number of compounds for their ability to stimulate synthesis of 1 series PGs in a prolactin-like manner. We wanted an agent which would do this without also stimulating formation of 2 series PGs. We had no success until on the advice of Mr. Owen Cooper, an unemployed person interested in our work, we tested antibiotics. It soon became evident that most antibiotics stimulated formation of the 1 or 2 series PGs or both and that penicillin had precisely the qualities we wanted (Horrobin, 1978c). It had actions consistent with stimulation of 1 series PGs in both blood vessels and platelets, and these effects occurred at concentrations readily achievable in human plasma.

A therapeutic trial was started with 10 severe chronic hospitalized schizophrenics who were known to relapse rapidly when withdrawn from phenothiazines. Their phenothiazine treatment was abruptly withdrawn and replaced by phenoxymethylpenicillin, 300 mg q.d.s. initially, progressively rising to 600 mg q.d.s. One patient relapsed, and one patient was withdrawn when he developed what seemed to be a penicillin allergy on the highest dose although he had had no problems with the lower doses. Of the other eight there were no clear-cut changes in their condition over a six-week period, i.e., the relapses known to occur in these patients failed to materialize, indicating that the penicillin was having an antipsychotic effect not far from that of the phenothiazines (Chouinard et al., 1978). The importance of this, of course, is that penicillin has been used for 30 years for long-term prophylaxis in rheumatic fever patients without any of the side effects of neuroleptic therapy. Hoffer and Osmond (1960) noted a similar antipsychotic effect of penicillin, but attributed it to the metabolite penicillamine because there seemed no rationale for therapy with an antibiotic.

The alternative approach to using a drug to increase synthesis of the 1 series of PGs is to increase the intake of PG 1 series precursors. The immediate precursor DGLA is not available for clinical use and is not present to any important degree in natural foods. However GLA, which in the body is readily converted to DGLA, is found in the seed oil of the evening primrose, Oenothera biennis. This oil contains 9 percent of GLA and 72 percent of linoleic acid and is an exceptionally rich source of essential fatty acids. Preliminary trials with the oil suggested that it was similar to penicillin; it could prevent relapse on withdrawal of neuroleptic therapy without causing any major improvement.

Vaddadi {1979) then tried the approach of administering both penicillin (250 mg q.d.s.) and evening primrose oil (2 x 0.65 ml capsules q.d.s.) to severe chronic hospitalized schizophrenics who had failed to respond well to a variety of neuroleptic regimes, including depot phenothiazine preparations. All other medications including night sedation were withdrawn on starting the penicillin and oil. To date no patient has become worse on this regime (six patients have now been treated for 16 weeks). Most have improved and in some the change has

been dramatic. For example, a severe paranoid schizophrenic, hospitalized for 20 years, who took no interest in personal hygiene, smoked 40 cigarettes a day, and repeatedly wrote and telephoned to the police and the Royal Family about the other patients and staff who were constantly listening to her thoughts and trying to murder her, became transformed. Her personal hygiene improved dramatically, smoking dropped to ten a day, letters and calls to the police and Royal Family stopped completely, and she displayed considerable amusement and insight when some of the letters were shown to her (Vaddadi, 1979). There seems to be no doubt that this combination has a therapeutic effect.

At present we are still in the very early stages of exploring the best ways in which to use this therapy, and it seems very unlikely that we have yet achieved an optimum dose regime. We had hoped to start a double-blind placebo-controlled trial, but our grant applications were turned down and so this has been delayed. At present it seems that the following regime may be optimal: penicillin 250 mg q.d.s.; evening primrose oil 6 or 8 x 0.65 capsules/day; zinc, 20-40 mg/day in order to insure that no deficiency is present. The only side effects noted have been mild bowel loosening and nausea on the first two to three days in some patients, but these pass off.

Conclusions

A rational approach to the pathogenesis and treatment of schizophrenia is outlined. This demonstrates that the main current competing theories are not mutually antagonistic, but are different aspects of the same problem. Based on the presumed pathogenesis, a treatment for schizophrenia was devised which is radically different from any hitherto used. Its apparent success strongly suggests that at least in outline the concepts on which it is based are substantially correct. Partly because of its sound theoretical base and partly because of its freedom from side effects, treatment with penicillin, evening primrose oil, and zinc promises to be a major advance.

Acknowledgment

Evening primrose oil was provided through Primrose Research Inc., 1538 Sher-brooke Street West, Montreal, Canada.

REFERENCES

ABDULLAH, Y. H., and HAMADAH, K.: Effect of ADP on PGE formation in blood platelets from patients with depression, mania and schizophrenia. Br. J. Psychiat. 127:591-595,1975.

BOULLIN, D. J., and ORR, M. W.: Effects of aspirin and prostaglandin E2 on secondary phase aggregation responses of schizophrenic patients treated with chlorpromazine. Br. J. Clin. Pharmacol. 3:929-933,1976.

CHOUINARD, G., ANNABLE, L, and HORROBIN, D. F.: An antipsychotic action of penicillin in schizophrenia. IRCS J. Med. Sci. 6:187,1978.

GUILLEMIN, R.: Endorphins: brain substances that act like opiates. New Eng. J. Med. 296:226-228,1977.

HOFFER, A., and OSMOND, H.: The Chemical Basis of Clinical Psychiatry, p. 223. C.C. Thomas, Springfield, 1960.

HORROBIN, D. F.: Dopamine supersensitivity, endorphin excess and prostaglandin E1 deficiency: three aspects of the same schizophrenic elephant Schizophrenia Bull. 4:487-488,1978a.

HORROBIN, D. F.: Lithium as a regulator of prostaglandin synthesis: relevance to manic-depressive psychosis and schizophrenia and to the mechanism of opiate action. In: Lithium: an International Symposium. Ed.: Cooper, T., Schou, M., Kline, N. S. Excerpta Medica, in press, 1978b.

HORROBIN, D. F.: Prostaglandins: Physiology, Pharmacology and Clinical Significance. Churchill Livingstone, Edinburgh; Eden Press, Montreal, 1978c.

HORROBIN, D. F.: Schizophrenia as a prostaglandin deficiency disease. Lancet 1:936-937,1977.

HORROBIN, D. F., ALLY, A. I., KARMALI, R. A., KARMAZYN, M,, MANKU, M. S., and MORGAN, R. 0.: Prostaglandins and schizophrenia: further discussion of the evidence. Psychol. Med. 8: 43-48, 1978.

KOSTERLITZ, H. W., and HUGHES, J.: Peptides with a morphinelike action in the brain. Br. J. Psychiat. 130:298-304,1977.

LAL, H.: Narcotic dependence, narcotic action and dopamine receptors. Life Sci. 17:483-496,1975.

LANGER, G., SACHAR, E. J., GRUEN, P. H., and HALPERN, F. S.: Human prolactin response to neuroleptic drugs correlate with anti-schizophrenic potency. Nature 266:639-640,1977.

MANKU, M. S., HORROBIN, D. F., KARMAZYN, M., and CUNNANE, S. C: Prolactin and zinc effects on vascular reactivity, possible relationship to dihomo-y-linolenic acid and to prostaglandin synthesis. Endocrinology, in press, 1979.

OWEN, F., CROW, T. J., POULTER, M., CROSS, A. J., LONGDEN, A., and RILEY, G. J.: Increased dopamine receptor sensitivity in schizophrenia. Lancet 2:223-226,1978.

SEELY, S.: The therapeutic effect of hemodialysis on schizophrenia: comments and further possibilities. Med. Hypotheses, in press, 1978.

TERENIUS, L.: Endorphins in psychotropic drug action. Presented at the 7th International Congress of Pharmacology, Paris, July 18,1978.

VAODADI, K. S.: Penicillin and evening primrose oil in schizophrenia. Submitted for publication, 1979.

WALFORD, E.: The Turkish bath in insanity. Br. Med. J. (2): 12-13, July, 1877.

ZIOUDROU, C, STREATY, R. A., and KLEE, W. A.: Opioid peptides derived from food: the exorphins. Submitted for publication, 1979.