# Histamine and Prostaglandins in Schizophrenia

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### Abstract

The interrelationship between histamine and prostaglandins may have some significance in the diagnosis and treatment of schizophrenia. A number of observations in the literature suggest that blood levels of histamine and prostaglandin E-1 (PGE-1) move concurrently in response to various agents. Their effects on physiological activity are also similar. Two theories on the etiology of schizophrenia, the theory of Pfeiffer and histamine the prostaglandin theory of Horrobin, may therefore be different sides of the same coin. On the basis of these theories the diagnosis and treatment of schizophrenia is discussed. All the cofactors used in the treatment of the low histamine type schizophrenic patient are also essential in the production of prostaglandin E-1 from essential fatty acids, which according to Horrobin are lacking in schizophrenia.

An interrelationship between histamine and prostaglandins, which may be of some significance in the etiology, diagnosis and treatment of schizophrenia is apparent from the literature. A number of indirect, but related observations suggest that blood levels of histamine and prostaglandin E-1 (PGE-1) seem to move in the same direction. Their effects on physiological activity when used as agents is also similar; substances which raise histamine tissue levels also raise PGE-1 tissue levels. Conversely, substances which lower histamine lower PGE-1. This relationship is summarized in Table 1.

Alcohol, known to release blood histamine, in small amounts activates the conversion of free dihomogamma-linolenic acid (DGLA) to PGE-1 (Horrobin, 1978a, 1980c, 1981b; Horrobin and Manku, 1980). Niacin and ascorbic acid presumably act at this same biochemical locus facilitating the formation of PGE-1 (Samuelson 1967, 1969). Copper activates the histamine degrading enzyme oxidase (histaminase). Indirectly diamine through the non-competitive inhibition of thromboxine A-2 (TxA2) formation, copper also lowers PGE-1 (Horrobin et al., 1978; Lee and Lands, 1972). Penicillamine chelates copper (Nicholson et al.,

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SUBSTANCE	HISTAMINE	PGE 1
ALCOHOL	+	( - larger amounts)
COPPER	-	-
PENICILLAMINE	+	+
FOLIC ACID	+	+ (PGE2+)
DILANTIN	-	-
ZINC	+	+
METHADONE	-	-
HISTIDINE	+	+
MELATONIN	?	+
PROLACTIN	+	+
PYRIDOXINE	+	+
NIACIN	+	+
ASCORBIC ACID	+/_	+
CHLORPROMAZINE	+	+
METHIONINE	-	-

Table 1

1966), potentially lowering the activity of histaminase. Penicillamine, along with zinc and prolactin, releases membrane bound DGLA ---a precursor of the prostaglandin 1 series (Horrobin et al., 1978b). Zinc is also important in the storage of histamine in the basophils and mast cells (Niklowitz, 1973) and the injection of prolactin in the anterior hypothalamus of male rats has been shown to selectively raise histamine (Alvarez and Donoso, 1981). Folic acid introduces the amidine carbon in histidine and increases both PGE-1 and PGE-2 by acting at the cyclo-oxygenase level (Hamberg and Samuelson, 1967). The antifolate agent phenytoin lowers histamine (Pfeiffer, 1975) and blocks the conversion of DGLA to PGE-1 (Karmazyn et al., 1977). Methadone lowers histamine (Green, 1967, 1978) and, representing an opiate, likely blocks the formation of PGE-1 (Horrobin, 1979c). Histidine, a precursor of histamine, may attenuate the effects of agents which decrease the formation of PGE-1 and enhances the effects of agents which stimulate the formation of PGE-1. (Horrobin, Oka and Manku, 1978). Pyridoxal phosphate is essential for the decarboxylation of histidine to histamine and also plays a basic role at two different steps in the formation of PGE-1 from its precursors (Horrobin et al., 1979).

Melatonin activates TxA2 which in turn mobilizes membrane stored DGLA to free DGLA — the immediate precursor of PGE-1 (Horrobin, 1980). It should also be mentioned that the diurnal rhythm of melatonin closely parallels the biological rhythm of histamine reactivity in normal humans (Reinberg et al., 1965). In addition to melatonin, the pineal contains high concentrations of histamine (Green, 1967), also histamine rich mast cells are believed to regulate function in the (pineal inervating) superior cervical ganglion (Behrendt et al., 1976). The relationship between histamine and pineal function is discussed later. Methionine forms taurine which has a lithiumlike action on PGE-1 formation, blocking the mobilization of membrane stored DGLA to free DGLA (Horrobin, 1978b; Horrobin et al., 1978).

Table 2 further touches upon the hypothetical relationship between histamine and PGE-1. Both histamine and PGE-1 formation are stimulated by phospholipase-A2 and ADP platelet stimulation (Abdulla and Hamadah, 1965; Sullivan and Parker, 1979). Both are reduced or blocked by epinephrine (Kafka et al., 1977) eicosatetraenoic acid (ETA, an analog of Arachidonic Acid) (Sullivan and Parker, 1979), imidazole (Needleman et al., 1977) and cromalyn sodium (PDR, 1984). PGE-1 and histamine inhibit slow reacting substance of anaphylaxis (SRSA) (Ryan and May, 1977), contract smooth muscles,

TION	HISTAMINE	PGE-I	
Stimulated by Phospholipase A2	+	+	
Stimulates cAMP	+	+	
Inhibits S.R.S.A.	+	+	
Contracts Smooth Muscle	+	+	
Increases Vascular Permeability	+	+	
Increased by ADP Platlet Stimulation	n +	+	
Sensitizes Pain Receptors	+	+	
Inhibits Release of Norepinephrine	+	+?	
Potentiates Histamine Edema	+	+	
Decreases Locomotor Activity	+	+	
Decreased by Epinephrine	+	+	
Reduces by B-Lymphocyte Activity	÷	+	
Inhibited by EICOSA TETRANOIC AC		+	
Decreased by Imidazole	÷	÷	
Release blocked by Cromolyn (INTA	L) +	+	

Table 2

# AGENTS & ACTIONS INVOLVING HISTAMINE and PGE-1 AGENTS OR ACTION HISTAMINE PGE-1

increase vascular permeability, sensitize pain receptors (Jaun, 1981; Jaun and Lembeck, 1974), inhibit the release of norepinephrine, potentiate histamine edema (Ryan and May, 1977), decrease locomotor activity (Nowak and Pile, 1977), and reduce B-lymphocyte activity (Horrobin et al., 1979).

# **Histamine Subtyping**

Pfeiffer subdivided the schizophrenias according to blood histamine, with char-Figure 1. Biochemical subtypes of schizophrenia according *to* Pfeiffer C.C. (1975). acteristic signs and symptoms. As shown by Figure 1, the majority of schizophrenic patients are represented by the low histamine type patient, while the high histamine group represents approximately 20 percent (Pfeiffer, 1975). Do low and high PGE-1 counterparts to the low histamine and high histamine schizophrenic exist? Indeed, there is impressive evidence to support the existence of the low PGE-1 biotype, and its remarkable resemblance to Pfeiffer's low



# **SYMPTOMS**

### Table 3

# LOW HISTAMINE & LOW PGE-1 COINCIDENCE OF BIOCHEMICAL

AND CLINICAL FINDING	GS
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]	LOW HISTAMINE	LOW PGE-1
	TYPE	TYPE
LOW HISTAMINE	· +	?
LOW PGE-1	?	+
LOW EPA	?	+
REDUCED WHEAL & Flair reaction	+	+
FEWER ALLERGIES &	COLDS +	+
NO NIACIN FLUSH	+	+
LOW INCIDENCE OF HEA	DACHES +	+
HIGH COPPER	+	+
LOW ZINC	+	+
HIGH AA/EPA RATIO	?	+

histamine schizophrenic subtype (Pfeiffer, 1976, 1977, 1978, 1979, 1980; Pfeiffer and Braverman, 1979, 1982; Pfeiffer and Iliev, 1972).

# Therapeutic Agents for Low Histamine/ Low PGE-1 Subtypes

Table 3 compares some of the biochemical and clinical findings between the low histamine type schizophrenic (Pfeiffer, 1972, 1975) and the low PGE-1 schizophrenic (Horrobin, 1977). Both biotypes may have reduced wheal and flair reactions, a low incidence of allergies and colds, a relative absence of niacin flush (Kunin, 1976), few headaches, high serum copper levels (Baron et al., 1982; Nicholson et al., 1966) and may also demonstrate low serum zinc (Horrobin, 1979a; Pfeiffer, 1975). Determining the blood and tissue levels of PGE-1, eicosapentaenoic acid (EPA), and arachidonic acid (AA) in a low histamine population, and histamine

	ETTEOTO ON.		
AGENTS	OW HISTAMINE TYPE	LOW PGE-1 TYPE	
FOLIC ACID	+	+	
VITAMIN C	+	+	
B6	+	+	
NIACIN	+	+	
ZN	+	+	
PENICILLAMINE	+	+	
HIGH PROTEIN DIET	+	+	
cis-LA (SAFFLOWER OIL	.) ?	+	
GLA (EVENING PRIMROS	EOIL) ?	+	
MAGNESIUM	?	+	
EPA (FISH OIL)	<b>*</b> 3	+	

THERAPEUTIC AGENTS FOR LOW
HISTAMINE and/or LOW PGE-1 SUBTYPES
EFFECTS ON:

blood levels and activity among low PGE-1 patients would certainly shed light on the hypothesis relating the low histamine schizophrenic to the low PGE-1 or PGE-1 responsive patient (Heleniak and Lamola, 1984a, 1984b).

As shown in Table 4, folic acid, vitamin C, Pyridoxine, niacin, zinc, penicillamine, and a high protein diet have beneficial therapeutic effects on the low histamine (Pfeiffer, 1975) and the low PGE-1 (Horrobin, 1981; Horrobin and Huang, 1983) type patients. Magnesium and the essential fatty acids Cis-linoleic acid, gamma-linolenic acid (GLA), and eicosapentaenoic acid (EPA) supplements are beneficial for the low PGE-1 patients and may be of benefit for the low histamine schizophrenics providing both patient types represent like or similar populations.

# Histamine and Schizophrenia

Considerable interest in histamine as a

therapeutic agent for the schizophrenic

occurred before the advent of pheno-thiazines (1954). Curiously, chlorpromazine (CPZ) was first used as an anti-histamine to counteract surgical shock presumed secondary to histamine release. CPZ, partial inhibitor а of methyltransferase, raises histamine (Wertheimer and Wertheimer, 1955). Subcutaneous injections of histamine were found to be effective therapy in schizophrenia; Marshal and Tarwater (1938) reported that 18 of 35 schizophrenic patients responded favorably. Hill (1938) reported therapeutic responses to intradermal histamine injection. From 1949-50, the Sacklers (1951) published several reports on histamine therapy in schizophrenias. Yamada and Takumi (1965) reported that small doses of histamine alleviated the effects of LSD in seven of nine normal subjects. Niacin, which may acutely release histamine and PGE-1, was used by Hoffer and Osmond during the 1950's to terminate the effects of LSD (Hoffer and Osmond, 1967).

### CLINICAL AND BIOCHEMICAL CLUES TO THE BETTER TREATMENT AND DIAGNOSIS OF SCHIZOPHRENIA

- 1. Pfeiffer's Differentiation of Low Histamine (Histapenia) and High Histamine (Histadelia) Schizophrenia.
  - a. Biochemical:

     diagnosis and treatment based upon blood histamine and basophil counts.
  - b. Signs and Symptoms:
    - Histadelia obsessions, compulsions, depression, suicidal ideation.
    - Histapenia paranoia, hallucinations.
  - c. Physical Attributes:

- Pain perception (low pain threshold in histadelia and high pain threshold in histapenia).

--- Sleep onset and duration (early onset and short duration in histadelia and the opposite in histapenia).

- Saliva flow (high in histadelia, low in histapenia).

- Libido (low in histapenics and high in histadelics).

### Horrobin — Differentiate Between Schizophrenic Patients and Patients with Temporal Lobe Seizure Disorders.

- a. EEG
- b. Niacin flush: absence of niacin flush to low doses of niacin (Kunin)

- 3. Platelet Studies
  - a. Effect of ADP on PGE formation in blood platelets. (Abdulla and Hamadah)
  - b. A reduced PGE-1 stimulated cAMP accumulation of platelets. (*Rotrosen*)
  - c. Platelet aggregation

     PGE-2 increases platelet aggregation and decreases cAMP.
     PGE-1 decreases platelet aggregation and

increases cAMP (Salzman).

- 4. T. Cells
  - a. Ratio between helper and suppressor cells; PGE-1 stimulates suppressor cells.
    b. Tcell/Bcell ratios.
  - 5. I Celly Deell Tatlos.
  - c. Effects of histamine on the differentiation and function of mature Tcells and Bcells.

### 5. Flair and Wheal Reaction

- a. Decreased in histapenia,
- b. Normal or increased in histadelia
- 6. Fatty Acid Precursors of Prostaglandins a. Omega-3 Oils
  - Alpha Linolenic acid (ALA)
  - Eicosapentaenoic acid (EPA)
  - b. Omega-6 Oils
    - --- Cis Linoleic acid (cLA)
    - Gamma Linolenic acid (GLA)
    - Dihomo-gramma Linolenic acid (DGLA)
  - Arachidonic acid (AA)
    AA/EPA ratio

Many have noted that schizophrenics have a low incidence of colds, allergies, asthma and low sensitivity to pain and cold. For example, Ehrentheil (1957) noted that the incidence of asthmas, hayfever and other allergic diseases in the insane was less than 0.1 percent compared to a figure of 3.5 percent for the population as a whole. Pfeiffer subdivided the schizophrenias according to blood histamine, the quantitative EEG and other signs and symptoms (Pfeiffer et al., 1972,1976,1982). Finally, there have been a few reports of schizophrenia-like psychosis following the vigorous administration of antihistamines, particularly the H-2 blockers (Roman, 1975).

### Histamine as a Neurohormone

Systemic histamine insensitivity has been implied from reports of a decreased incidence of asthma and allergic disorders among schizophrenic patients. Starting from Whithorn (1963) to Verghese and Thomas (1972), 12 studies reported a diminished cutaneous response in schizophrenic patients to intradermal injections of histamine. Histamine has a non-uniform distribution in the CNS, and is stored in subcellular fractions containing synaptisomes (Green, 1967). The specific enzymes for its synthesis (histidine decarboxylase), and degradation (methylation pathways) are present in brain tissue (Green, Johnson and Weinstein, 1978). In 1961 it was observed that in schizophrenia there was less urinary excretion of methyl imidazole acetic acid-the major metabolite of brain histamine — and more conjugated imidazole acetic acid (Kobayashi and Freeman, 1961). Histamine stimulates adenosyl cyclase activity which is blocked by specific antagonists (Schwartz, 1977). In summary, specific neurons are responsive to histamine which is found in all nerve cells with the highest concentration in the post-ganglionic sympathetic nerves.

# Mast Cells and Basophils

The absolute basophil count correlates with blood histamine levels, since mast cells and basophils are the main repositories of nonneuronal histamine (Pfeiffer, 1972; Pfeiffer et al., 1972a). LeBlanc and Lemieux (1961) found a relative scarcity of mast cells in schizophrenic patients, and patients who responded to therapy showed an increase in the number of mast cells. Mast cells may exert a regulatory function in superior cervical ganglion transmission

superior transmission (Behrendt et al., 1976), and indirectly or perhaps directly on the histamine-rich pineal gland. According to Horrobin the biological defect in schizophrenia may be related to pineal deficiency, which in turn would result in PGE-1 reduction. Horrobin suggested that a superior cervical ganglionectomy may be beneficial in schizophrenia, since pineal melatonin output is inhibited by inervation originating from the superior cervical ganglion (Horrobin, 1979c). The finding that the histamine-rich mast cells may regulate function in transmission in the superior cervical ganglion (Behrendt, Lindl and Cramer, 1976) presents another interesting but unexplored — relationship between prostaglandins, the pineal, the superior cervical ganglion, and histamine. Mast cells, which are found in all tissues, were found to be relatively scarce in the skin of schizophrenic patients. Patients who responded to therapy showed an increase in the number of mast cells (LeBlanc and Lemieux, 1961). What is relevant is that mast cells in tissues are sensitive to hormones, particularly corticosteroids. The secretion of corticosteroids is under central control, and levels reportedly increase during schizophrenia and decrease after treatment with penothiazines (Green, 1967). Thus, a disturbance in histamine metabolism may result in secondary disturbances in pineal function which in turn may result in acute and/or chronic pineal dependent metabolic alterations. For example, it was recently demonstrated that melatonin inhibited dopamine release from rat hypothalamus and the inhibitory effect on dopamine release by melatonin may stem from the reduction of calcium entry into the pre-synaptic nerve endings (Nava Zisapel and Moshe Laudon, 1983). Arendt and colleagues noted that in long on immunoreactive human term studies melatonin, that colchicine and melatonin may compete for the same binding sites (Arendt et al., 1979). Schliwa (1979) noted that low concentrations of colchicine may have melatonin-like actions. In agreement with these observations.

Horrobin noted that low concentrations of colchicine have actions which are consistent with a selective increase in either the synthesis or the biological activity of throm-boxine-A2 (Horrobin, 1980a). Histidine, the amino acid precursor of histamine, seems necessary for the optimal action of colchicine on thromboxine-A2 (Horrobin, 1978). Imidazole, a selective inhibitor of thromboxine-A2 synthesis (Needleman et al., 1977), inhibits thromboxine-A2 formation selectively, and leads to a 2.3 fold rise in outflow of other prostaglandins (Wolfe et al., 1979). Selective inhibition of thromboxine-A2 formation from endoperoxides caused a great increase in the production of PGF-2-alpha from prostaglandin-E2 and labelled arachidonic acid (Nijkamp, et al., 1977). Horrobin states that thromboxine-A2 enhances PGE-1 formation and inhibits arachidonic acid mobilization via feedback interaction (Horrobin, 1979). In regard to this possible interaction between histamine, PGE-1 and the pineal gland it should be noted that Cabut and Vincenzi demonstrated that PGE-1 stimulated mast cell degranulation with histamine and heparin release (Cabut and Vincenzi, 1967). Thus PGE-1, under the experimental conditions, may act as a second messenger in histamine activation.

Methionine worsens histapenic schizophrenia by lowering blood histamine (Pfeiffer and Braverman, 1979); and in terms of Horrobin's hypothesis it may also be related to the fact that methionine gives rise to taurine, which has a lithium-like action on PGE-1 (Horrobin et al., 1978b).

# Role of Histamine-Dopamine Interaction in Schizophrenia

The sagittal section of a rat's brain in Figure 2 demonstrates dopamine and histamine pathways (Cooper, Bloom and Roth, 1974). The nucleus accumbens of the septal area is near the olfactory tubercle. The mesostriatal pathway originates in area 8 of midbrain and projects to the caudate puta-men. The mesolimbic system originates in area 10 of the midbrain and projects to the nucleus accumbens of the septum. The nucleus accumbens is the area of the mesolimbic pathway where dopamine and histamine have complementary and modulatory functions (Chronister and DeFrance, 1982). This modulated hippocampal activity influences a wide variety of cortical and subcortical areas (Chronister et al., 1981; Chronister and DeFrance, 1981). Dopamine originates in the ventral tegmental area and

Figure 2. A sagittal section of a rat's brain showing histamine and dopamine pathways (Cooper, Bloom, Roth, 1974).



initiates impulses via the medial forebrain bundle to the nucleus accumbens. The histaminergic pathways travel from the original source in the rostral mesencephalic reticular formation and caudal diencephalic areas of mammalary bodies via the medial forebrain bundle to the nucleus accumbens, and also project to the hippocampus (Chronister et al., 1982) The physiological data of Perry (1979) suggest that histamine works through histamine 2 receptors in the nucleus accumbens, perhaps potentiating the effects of gamma aminobutyric acid (Perry et al., 1979).

Crow and Deakin suggest that the nucleus accumbens is a possible site of anti-psychotic drug action; as they have shown, all neuroleptics exert their therapeutic effects through dopamine blockage in the nucleus accumbens (Crow and Deakin, 1979).

Chronister and DeFrance noted in 1982 that there is an attentional deficit in schizophrenias caused by an imbalance in dopamine and histamine modulation of afferent hippocampus activity in the nucleus accumbens. They proposed that some aspects of attentional deficits in schizophrenia can be accounted for by a defect in this filtering system, or by an imbalance in dopamine-histamine systems. Dopamine effects can be mimicked by a net decrease in histamine receptors, or an increase in the histamine degradation; thus allowing a relative excess of dopamine (Chronister and DeFrance, 1981, 1982; Chronister et al., 1981,1982).

# Histamine, Abnormal Capillaries and Schizophrenia

Histamine is important in the production and functioning of capillaries, and this may have an important role in schizophrenia. Abnormal capillaries in schizophrenics were confirmed in a study of capillaries in the fingernail beds of schizophrenics. Maricq and Alson of Lyons VA Medical Center discovered that manv schizophrenics lack true hairpin-shaped capillaries (Maricq and Alson, 1963a, 1963b). They found instead a sub-capillary plexus, a structure that normally disappears early in life. Associated with the plexus they found a glossy skin on the dorsal side of the terminal phalanx and sweat ducts that are long and straight rather than coiled as are normal ones. Capillary abnor-

malities in schizophrenic patients also correlated with blood stasis, low systolic and diastolic blood pressure, and low basal metabolic rates (Wertheimer and Wertheimer, 1955). Low hand-skin temperature (84.6-90.8 F) was found in patients lacking plexus and response to hot and cold water were opposite to those of normal capillaries — indicating sympathetic nervous system abnormalities (Schendi et al., 1969). Photo-microscopic evaluation suggested cooling resulted in vasodilation of the plexus instead of constriction and heat in constriction. The abnormal capillaries may indicate a vegetative rearrangement, perhaps mirroring an abnormality of ectoderm in brain tissue (Hauptmann and Myerson, 1948). The anatomical and functional rearrangements in the capillaries are not confined to the cutaneous vascular bed; for example Ingvar and Fransen (1974) demonstrated that the lower the resting blood flow to the frontal lobes relative to the post central regions, the more severe was the psychotic process among chronic patients. Green and Johnson (1978) considered that the abnormal appearance and response of blood vessels are due to a failure of histamine release from mast cells, or a failure to synthesize nascent histamine. Histamine influences and activates adenylate cyclase in brain capillaries, and may contribute to the growth and maturation of capillaries and other tissues (Schayer, 1971).

# **Prostaglandins and Schizophrenia**

In 1980, Mathe reported an elevation of PGE in cerebral spinal fluid of schizophrenics, but did not distinguish between PGE-1 and PGE-2 (Mathe et al., 1980). Later Mathe found an elevation of PGE-2 and low PGE-1 in the cerebral spinal fluid of schizophrenics (Mathe, 1981). Most drugs effective in schizophrenia raise prolactin. Prolactin in turn may stimulate the formation of PGE-1 from its precursor -DGLA. The stimulation of prolactin seems to be a better predictor of antipsychotic action than any other test (Clemins, Smalstig and Shaar, 1974). Schizophrenics are more resistant to pain; low levels of PGE-1 and histamine, both of which are lowered in the brain by morphine (Collier and Roy, 1974), are accompanied by low sensitivity to pain. We also know that the low histamine patients are relatively pain-

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insensitive (Pfeiffer, 1975). Schizophrenics may show improved mental states during fever; fever raises brain PGE-1 (Horrobin, 1979). This indirect evidence suggests that PGE-1 levels or activity may be low in schizophrenia, and that the levels of arachidonic acid and the 2-series prostaglandins may be high.

# **Direct Evidence of PGE-1 Deficiency in Schizophrenia**

Abdulla and Hamada (1975) observed that the platelets from schizophrenics failed to make PGE-1 in response to ADP, while those from normal subjects and affective disorder patients made substantial amounts (400-500 percent increase in ADP). Also PGE-1 stimulation of platelet cyclicAMP from schizophrenics was blunted compared to the controls (Rotrosen et al., 1978). It was demonstrated that this blunted response to PGE-1 by platelets of schizophrenic patients was due to a membrane associated abnormality of the receptor system and not adenylate cyclase itself (Garver et al., 1982). Red cells may be deficient in both DGLA and linoleic acid, and high in arachidonic acid (Hitzmann and Garver, 1981). Mathe (1981) found an elevation of PGE-2 and low PGE-1 in the CSF from schizophrenics. This direct evidence strongly suggests that schizophrenics are deficient in linoleic acid, GLA,

DGLA and the 1-series prostaglandins, but have an excess of arachidonic acid and its two series prostaglandin derivatives (Horrobin and Huang, 1983). A lack of PGE-1 could therefore lead to an apparent excess of dopamine. An excess of dopamine is currently the most popular idea concerning the mechanism of schizophrenia. Normally PGE-1 inhibits ADP induced platelet aggregation. Kaiya found that this inhibiting effect of PGE-1 was reduced in platelets from schizophrenic patients (Kaiya et al., 1983). This same group reported that three of six schizophrenics responded to intravenous PGE-1 (Kaiya, 1984). This report, reminiscent of histamine therapy, adds to the direct evidence supporting the idea that PGE-1 plays a role in schizophrenia.

### **Omega 6 and Omega 3 Oils**

Figure 3 shows the metabolic pathways of two essential fatty acids. The one on the left is the omega-6 series which forms the precursors of DGLA and the 1-series prostaglandins, and also arachidonic acid and the 2-series prostaglandins. On the right are the omega-3 oils and their derivatives which form the 3-series prostaglandins.

Rudin has reported that linseed oil which contains alpha-linolenic acid (omega-3) is



effective in cases of intermittent schizophrenia, manic depression, and phobic disorders. He also gives nutrients such as niacin, Pyridoxine and zinc to convert the substrate essential fatty acids to prostaglandins. Rudin states that if enough of the substrate is given, the patient will need less vitamins and minerals to convert the essential fatty acids to prostaglandins; thus mega doses can be avoided (Rudin, 1982).

Members of both series are important in brain structure and for prostaglandin formation. Normally the desaturase enzymes which metabolize essential fatty acids have higher affinity for the omega-3 series. It is proposed that in schizophrenia a mutant desaturase is present which prefers omega-6 oils (Horrobin and Huang, 1983). This would account for the low levels of Cis-linoleic acid, GLA and DGLA and also account for the high levels of arachidonic acid and alpha-linolenic acid found in schizophrenia (Obi and Nwanze, 1979). Omega-9 oils such as oleic acid (olive oil) greatly reduce the desaturation of DGLA to arachidonic acid (Lowry and Tinsely, 1966). It should also be noted that Culp and Titus (1979) found that EPA inhibits the conversion of AA to its 2-series products. The conversion of linoleic acid to GLA is susceptible to interference by many factors - these include saturated and trans fatty acids, processed vegetable oils

# Figure 4. Blocking factors and the formation of PGE-1 from its precursors.

and large amounts of alcohol. Also cancer, aging, viruses and radiation interfere with GLA production. This blockade can be bypassed by giving GLA or Evening Primrose Oil directly (Horrobin, 1983).

While Horrobin, Rudin and others have found low Cis-linoleic acid blood levels in schizophrenia, Pecora found high levels of cislinoleic acid in chronic schizophrenic patients who had high fasting insulin levels and elevated urinary kryptopyrole (Pecora, 1983). Insulin, pyridoxal phosphate, zinc and magnesium are required for the delta-6-desaturase to convert cis-linoleic acid into GLA (Horrobin, 1983). Pyroluric schizophrenic patients, with elevated urinary kryptopyrole (Pfeiffer et al., 1972a) may have a disturbance in delta-6 desaturase and elevated levels of cis-linoleic acid since the important cofactors vitamin B6 and zinc may be differentially lacking in these patients (Pfeiffer et al., 1974).

Figure 4 shows blocking factors between stored DGLA and free DGLA and between free DGLA and PGE-1. Methadone, dilantin, lithium, parlodel and methionine — block the formation of PGE-1 and also are used in the treatment of histadelia (high histamine). Methionine, which aggravates histapenia, in large doses inhibits the uptake of histidine — the precursor of histamine (Pfeiffer, 1984).





Figure 5. Various co-factors required in the formation of PGE-1 from its precursors.

# **Co-factors in the Formation of PCs**

Summarizing (Fig. 5), the co-factors required in the conversion of PGE-1 from cis-Linoleic Acid are vitamin B6, zinc and magnesium to form Gamma-Linolenic Acid. If this primary pathway is blocked, it can be bypassed by giving GLA as Evening Primrose Oil directly. GLA is then converted to di-hommo-gamma linolenic acid via elongase which also requires vitamin B6. It is then stored in cellular membranes and must first be mobilized for conversion to PGE-1. Factors which tend to mobilize stored GLA, or the so-called "Releasing Agents" include zinc and prolactin.

Thromboxane A2, which can be stimulated by melatonin or small amounts of colchicine which actions in turn are enhanced by histidine, may act as a DGLA releasing factor. Also, penicillin (Vaddadi, 1979; Chouinard, Annable and Horrobin, 1978), penicillamine (Nicholson et al., 1966), and Captopril (Parmigiani, 1982) — all of which have been found to be beneficial in the treatment of schizophrenia may also act by mobilizing membrane-bound DGLA. Folic Acid may also be a co-factor for the cyclo-oxygenase stage (AA and DGLA conversion to endoperoxides) (Horrobin, 1979b). If Folic Acid is lacking, PG formation will diminish. Niacin and Ascorbic Acid are needed to convert free-DGLA to PGE-1. To decrease PGE-2 and increase PGE-1, oleic acid will block the formation of AA from DGLA. Alpha-linolenic acid or linseed oil — which forms EPA — or fish oils containing EPA, block the conversion of AA to the 2-series prostaglandins.

### **Conclusion and Summary**

This paper demonstrates an interrelationship between histamine and prostaglandins, which may have some significance in the diagnosis and treatment of schizophrenia. A most striking observation is that histamine and prostaglandin E-l (PGE-1) levels seem to move in the same direction. That is, substances which raise histamine also raise PGE-1. Conversely, substances which lower histamine also lower PGE-1.

Two important and independent theories involving the etiology of schizophrenia are disturbances of histamine metabolism and disturbances in prostaglandin metabolism, notably PGE-1. Some of the substances that raise both histamine and PGE-1 are small amounts of alcohol, penicillamine, folic acid, zinc (storage of histamine), histidine, prolactin, Pyridoxine, niacin and chlorpromazine Substances that lower both histamine and PGE-1 are copper, dilantin, methadone and methionine. Histamine and PGE-1 are stimulated by phospholipase-A2, increased by ADP platelet stimulation, decreased by imidazole and epinephrine, and inhibited by eicosa-5, 8, 11,14-tetraoic acid ("ETYA" — an analog of arachidonic acid).

Both histamine and PGE-1 stimulate cyclic AMP formation, contract smooth muscle, increase vascular permeability, sensitize pain receptors, inhibit the release of norepinephrine, potentiate histamine edema, decrease locomotor activity, and reduce B-lymphocyte activity.

In regard to the coincidence of clinical and biochemical findings among the low histamine (histapenic) and the low PGE-1 patients, both low histamine and low PGE-1 patients have reduced wheal and flair reactions, fewer allergies and colds, low incidence of niacin flush, low incidence of headaches and may have elevated levels of copper and low levels of zinc.

Therapeutic agents for both the low histamine and low PGE-1 type patients are similar. Folic acid, ascorbic acid, niacin, zinc, Pyridoxine, penicillamine, high protein diets and neuroleptics which raise histamine (e.g. through partial inhibition of methyl trans. ferase) and also raise PGE-1 (via prolactin elevation) are effective in the treatment of both types of schizophrenia. The essential fatty acids (cis-linoleic acid or safflower oil, GLA or Evening Primrose Oil, alpha-linolenic acid or linseed oil, and EPA or fish oils) considered to be effective in the low PGE-1 type patients, may also be effective adjuncts in the treatment of the low histamine patient. Evidence was given for histamine being etiological in schizophrenia. Mast cells (storage sites of nonneuronal histamine) are relatively scarce in the skin of schizophrenics, and increase in response to therapy. In the nucleus accumbens, histamine works through the histamine (H2) receptors. The nucleus accumbens is believed to be a possible site of antipsychotic drug action. In 1982 Chronister and DeFrance noted that there may be an attentional deficit in schizophrenia caused by an imbalance in dopamine and histamine modulation of afferent hippo-campal activity in the nucleus accumbens. Dopamine effects can be mimicked by a net decrease in histamine receptors or an increase in the histamine degradation, thus causing a relative excess of dopamine.

Support for decreased PGE-1 and elevated PGE-2 in schizophrenia was reported by Mathe in 1981 in his studies of prostaglandins in the CSF from schizophrenic patients. Abdulla and Hamada observed in 1975 that platelets from normals and affective disorders made substantial amounts of PGE-1 in response to ADP, while in schizophrenics the platelets failed to produce PGE-1 in response to ADP stimulation. Hisanabu Kaiya found reduced inhibition of platelet aggregation by PGE-1 in platelets from schizophrenics exposed to ADP. Recently, Hisanabu Kaiya reported three of six schizophrenic patients responded to intravenous PGE-1.

Rudin has found alpha-linolenic acid rich linseed oil and EPA rich fish oils to be effective in schizophrenia; EPA blocks the conversion of arachidonic acid to the 2-series prostaglandins.

Horrobin proposes that a mutant fatty acid desaturase present in schizophrenia prefers the Omega-6 series over the Omega-3 series. This would account for the low levels of cis-Linoleic acid, GLA and DGLA and the high levels of arachidonic acid and alpha-linolenic acid found in schizophrenia. We suspect that the "pyroluric patient", representing а sub-group of schizophrenic patients highly dependent upon zinc and Pyridoxine, may also have a "block" in delta-6-desaturase and therefore elevated cislinoleic acid blood levels.

Methadone, phenytoin, lithium, bromocryptine and methionine block the formation of PGE-1 and are also used in the treatment of histadelia (high histamine type patients). Methionine, which aggravates histapenia (low histamine type), in large doses inhibits the uptake of histidine (the histamine precursor) in the brain.

In summary, all the co-factors that Pfeiffer uses in the treatment of the low histamine type schizophrenic patient are also essential in the production of prostaglandins from the essential fatty acid substrates that are lacking in schizophrenia according to Horrobin, Rudin and others.

By distinguishing the schizophrenic subtypes clinically and biochemically, according

to the low and high histamine classifications, and the low and high PGE-1 classifications and related prostaglandin disturbances, and by using all the co-factors and essential fatty acids substrates that are required to correct the deficiencies or disturbed metabolism, we may be able to improve the functioning of the individual schizophrenic.

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