Could Dietary Manipulation Modify Schizophrenic Behavior?

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To this day we do not know whether schizophrenia is a unitary disorder or whether it is the final manifestation and outcome of a variety of independent diseases with a final common pathway. Whatever the case may be, we do know that hereditary factors play a major role in the development of schizophrenia or the schizophrenias. There is a certain constitutional propensity which is genetically determined and which makes the subject prone to develop the disease. The studies of Kety et al of schizophrenia in biological and adoptive families appear to confirm this fact.[17] They proved, beyond any doubt, the hereditary nature of the disease.

Genetic factors, which accordingly play a major role in the development of schizophrenia, are either responsible for the disease itself or are simply able to pass on the propensity to develop the illness. Since genes are known to operate through biochemical means, then it must follow that schizophrenia is the result of some biochemical injury or fault.

In the field of biochemistry, many theories have been proposed; but it is in the area of neurotransmitters that most of the positive findings have been made.

Neurotransmitters are the dynamic components of neuron tissue. Furthermore, a neurotransmitter is one functionally significant component that identifies a particular set of neurons.[7] Since the disorder in schizophrenia is presumed to affect a circumscribed set of neuron systems, and since the disturbance is believed to be biochemical in nature, then it is quite plausible that it involves a specific neurotransmitter system.

Over the past few years, recognition of the importance of "transmitter balance"[9] in regulating normal behaviour has naturally led to the concept of "transmitter imbalance" as the ultimate basis of abnormal behaviour.[20] Such transmitters may act either by conveying messages directly or by modulating other means of transmission.

At the level of the synapse, transmission occurs by the outpouring of a quantum of the chemical. A decrease in the optimum quantity of the chemical may fail to effect a transmission, while a pathological increase may also, paradoxically, fail to effect the transmission through the occurrence of a depolarizing block. A delicate balance, therefore, has to be maintained. Imbalance, on the other hand, may arise from diverse primary causes such as inherited metabolic abnormalities, degenerative processes, viral infections, auto-immune mechanisms, drugs, nutritional factors, and others. Thus, in the case of schizophrenia, the concept encompasses the possibility of multiple etiologies, all leading to a final common pathway.[20]

The number of putative Central Nervous System (CNS) transmitter candidates now exceeds 40.[14] The ones, however, that appear to be somehow implicated with schizophrenia are Dopamine (DA) and Norepinephrine (NE).

Dopamine

The suggestion that some disturbance of dopaminergic function exists in schizophrenia stems largely from the following observations.

(1) High doses of Dopamine-releasing agents (such as amphetamines and methyl phenidate) can precipitate, in normal subjects, a psychosis closely resembling paranoid schizophrenia.[5 11 8]

(2) More impressive, however, is the ability of low doses of amphetamines to exacerbate schizophrenic symptoms.[15 2]

(3) Levodopa, which acts almost wholly through DA, can also worsen schizophrenic

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symptoms.[3]

(4) The neuroleptic drugs possess the property of blocking DA receptors with a potency that parallels their therapeutic efficiency.[25]

(5) Neuroleptic drugs, which are known to block DA receptors, not only ameliorate the symptoms of schizophrenia but can also reverse the action of amphetamines.[7]

(6) The most frequently reproducible finding in post-mortem schizophrenic brains is an increase in the total number of DA receptor binding sites observed in the caudate, nucleus accumbens, and olfactory tubercle.[20 25]

Norepinephrine

The role of NE in the etiology of schizophrenia is not as clear as that of DA. NE is known to play a major role in behaviours such as feeding, aggression, locomotion, memory, reward, and others. At a more intrinsic level, it may be a neuromodulator rather than being a neurotransmitter. In schizophrenia, it is possible that anhedonia, withdrawal, and flatness of affect represent an insufficiency of NE at its synapses.[17] An abnormal increase may also result in the same outcome through the occurrence of a depolarizing block.

It may be surmised from the above considerations that both DA and NE have a decisive role to play in the development of schizophrenia.

Norepinephrine is derived from tyrosine via 3,4-dihydroxyphenylalanine. Another intermediate in this conversion is 3,4-dihydroxyphenylethylamine, usually called dopamine.[18] Tyrosine is a nonessential amino acid, but it is made by animals from the essential amino acid phenylalanine.[19] In nature they are also usually found together.

We can, therefore, safely assume that Phenylalanine (PHE) is the real precursor of both DA and NE. It is an essential amino acid and so cannot be manufactured in the body. Like other amino acids, it cannot, also, be stored in the body. An adequate and continuous supply has to be provided in the diet. Furthermore, the concentration of PHE in the blood, relative to other large neutral amino acids (LNAA), appears to reflect its availability to the CNS. This has been shown by Wurtman et al,[27] who based their conclusions on the following criteria:

(1) the lack of significant feedback control of plasma levels of the precursor;

(2) the lack of a real blood-brain barrier for the precursor, to control its influx into, or influx from, the CNS;

(3) the existence of a low affinity between (and thus unsaturated) transport system, mediating the flux of the precursor between blood and brain;

(4) low affinity kinetics for the enzyme that initiates the conversion of the precursor to the transmitter;

(5) the lack of end-product inhibition of the enzyme, in vivo, by its ultimate product, the neurotransmitter.

Furthermore, amino acids of similar size share a common carrier, and within a given transport group, the individual amino acids compete with each other for available carrier sites and thus brain uptake.[10] Consequently, the brain levels of a LNAA should rise when either its blood levels rise or the blood levels of one or more of the other LNAA competitors fall. The brain levels of that same LNAA will fall when either its blood level falls or the blood concentrations of the other LNAA's rise.

Tryptophan (TRP) is a LNAA; it is an essential amino acid; and it is also a precursor of the neurotransmitter 5-hydroxytryptamine or Serotonin. Variation of its availability in the diet has been found to modify behaviour.

A depressive psychosis is one of the characteristic signs of the Tryptophan-Niacin deficiency disease, pellagra. It is most likely that this disease is not a direct result of Niacin deficiency per se, and is not due to depletion of brain pools of nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate but rather to a deficiency of Tryptophan. The very low circulating concentrations of Tryptophan in pellagrins will result in considerably reduced synthesis of the neurotransmitter Serotonin. However, the psychosis does respond to Niacin therapy, perhaps because there is feedback inhibition of Tryptophan oxygenase by the nicotinamide nucleotide coenzymes, and hence oxidative metabolism of Tryptophan

will be reduced, and a greater amount will be available for reuptake into the brain and synthesis of Serotonin.[4]

An increase in the availability of Tryptophan, on the other hand, has also been shown to affect behaviour. Its administration has been reported to act as a hypnotic[12] and an antidepressant.[6] Oral administration of Tryptophan has been reported to reduce sleep latency and to increase subjective sleepiness in subjects with long sleep latencies.[13] A single, one gram dose was insufficient to diminish the times required for subjects to attain stage one or stage two sleep; however, people who took this dose with a carbohydrate tended to have the shortest sleep latencies.[1] This is because the carbohydrate will stimulate the production of insulin, and insulin in its turn encourages the uptake of LNAA other than Tryptophan into muscles, thus allowing Tryptophan to pass freely through the blood-brain barrier without competition of other LNAA's.

Availability of TRP in the diet thus appears to influence behaviour — an increase counteracting depression and promoting sleep, while a decrease inducing a psychotic depression.

PHE is in many ways analogous and comparable to TRP. An increase in the availability of PHE is known to lead to the condition of phenylketonuria, while a decrease in its availability will result in reduced production of DA and NE; and if, as is apparent, schizophrenic behaviour is the result of some lesion affecting the DA and NE neurotransmitter systems, then a reduction in the availability of PHE would be expected to modify schizophrenic behaviour.

The PHE requirements of human adults was estimated by Rose and his associates to be about 16 milligrams per kilogram body weight per day.[22] Close to 75% of human adult requirement for PHE can, however, be met by Tyrosine (TYR).[23]

A diet poor in both PHE and TYR is given to phenylketonuric children and phenylketonuric pregnant mothers. Such a diet will acutely limit the availability of both PHE and TYR to the brain. It has been found to be quite safe and has proved to be without ill effects. If we, therefore, provide such a diet, which is quite safe, to schizophrenic patients, then by limiting their intake of PHE and TYR we should be able to modify their schizophrenic symptoms. A preliminary trial, using such a diet, was done and the results were quite encouraging and warrant further studies.[24]

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