

The Genetics and Neurochemistry of Schizophrenia and Addiction: Enhanced Options for Treatment Using Nicotinic Acid (Vitamin B₃)

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Abstract *The role of oxidative stress has been reviewed in a variety of psychiatric disorders, particularly schizophrenia and alcoholism (index cases), which are associated with deficiency of protective enzymes: superoxide dismutase and catalase, respectively. The reported effectiveness of nicotinic acid in the treatment of schizophrenia and alcoholism appears to be due to enhanced levels of nicotinamide adenine dinucleotide (NAD), thereby opposing the deleterious effects of genetically determined neuronal oxidative stress, arguably an important final common pathway in schizophrenia and alcoholism. The potential for nicotinic acid supplementation to remit schizotypy (schizoid traits) in family members containing an index case has been proposed and such a case is described. This report hints at the potential role of nicotinic acid in remitting an array of psychiatric disorders linked genetically and biochemically to schizophrenia.*

Introduction

Two major facts have emerged from research into the genetics of psychiatric disorders and into the neurochemistry of psychiatric disorders. Firstly, gene analysis has demonstrated genetic overlap encompassing the following disorders: autism spectrum disorder (ASD), attention deficit-hyperactivity disorder (ADHD), bipolar disorder, major depressive disorder, and schizophrenia.¹ The genetic expression of dopamine- and cyclic-AMP-regulated phosphoprotein of molecular weight 32,000 (DARPP-32) is associated with enhanced cognitive performance yet appears to contribute to the risk of schizophrenia² and is linked to bipolar disorder.³ Seeing as substance abuse is found in about 50% of schizophrenics, the DARPP-32 haplotype may also predispose to this disorder. Family studies have confirmed such overlaps, e.g.,

the excess risk of ASD in families affected by schizophrenia or bipolar disorder.⁴ In other words gene analysis and family studies reinforce the view of overlap of gene expression in what have been regarded as clinically distinct psychiatric disorders.

Secondly, a common biochemical finding in several of these disorders is oxidative stress.⁵ The term "oxidative stress" is meant to convey a relative incapacity to eliminate (by means, for example, of efficient redox systems) potentially toxic products of cellular oxidation, such as hydrogen peroxide and the superoxide radical.

Are there overlaps in other psychiatric disorders? There are clinical similarities between juvenile schizophrenia and autism. For example, pre-morbid characteristics of juvenile schizophrenia include defects in communication, social relatedness and mo-

tor development that are features of ASD. Furthermore ASD patients may become deluded if stressed and alcoholics may hallucinate during delirium tremens, brought on by withdrawal from alcohol.

Biochemical Overlap

What about the biochemistry of these genetically related disorders? Biochemical oxidative stress has been described in schizophrenia,⁶⁻⁸ autism,⁹ depression,¹⁰⁻¹² and alcoholism.^{13,14} The data in the case of alcoholism does not permit a clear conclusion as to the role of oxidative stress, seeing as oxidative stress may be a cause or a result of alcoholism or a combination of both. Notwithstanding this, the question is posed: Since the same genes (given the "right" environmental milieu) tend to express a variety of psychiatric conditions, do they do so by generating oxidative stress and is the accumulation of reactive oxygen species a major final common pathway in psychiatric disorders?

Cells normally protect themselves against the accumulation of the toxic oxidation products such as the superoxide radical by means of the following enzymes (**Figure 1**, below):

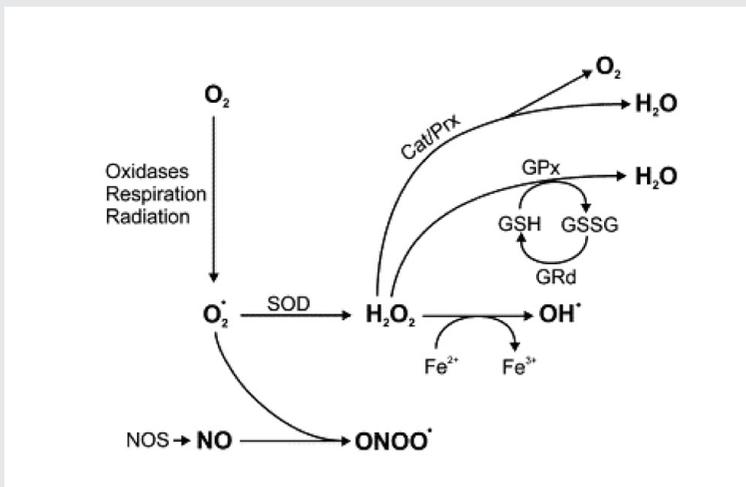
1. Superoxide dismutase.
2. The glutathione redox system, i.e., glutathione reductase and glutathione oxidase.
3. Catalase.

However, these enzymes need to be supported by:

1. An adequate supply of NAD (Nicotinamide Adenine Dinucleotide) and an intact $\text{NAD} \leftrightarrow \text{NADH}$ redox system.
2. An intact electron transfer system (cytochrome chain).

Any interruption to this chain of the elimination of oxidation products is liable to lead to a build-up of intracellular oxidation products (e.g., superoxide and hydrogen peroxide) and so give rise to intracellular damage. NAD and its reduced counterpart (NADH) comprise a critical redox system. This system passes energy-generating electrons from the

Figure 1. Simplified schematic overview of reactive oxygen species production and scavenging. O_2 , oxygen; O_2^- , superoxide; H_2O_2 , hydrogen peroxide; OH^\cdot , hydroxyl radical; NO , nitric oxide; ONOO^\cdot , peroxynitrite; NOS , nitric oxide synthase; SOD , superoxide dismutase; GPx , glutathione peroxidase; GRd , glutathione reductase; GSH , reduced glutathione; GSSG , oxidized glutathione; Cat , catalase; Prx , peroxiredoxin (From Schreibelt et al;²¹ adapted from Maher and Schubert;²² Used with permission from Elsevier)



enzyme systems described above (SOD, glutathione redox system and catalase), from glycolysis and Krebs's cycle onto the electron transport system (ETS) for the purpose of generating adenosine triphosphate (ATP), the "Energy Currency" of the cell. The interface between NAD and the ETS constitutes a biochemical bottleneck with very little redundancy with respect to the supply of the nicotinic acid component of NAD.

The Role of Nicotinic Acid

Dietary levels of nicotinic acid must be adequate to contribute to the synthesis of NAD for this delicately balanced oxidizing system to work properly. Failing that, tryptophan can be converted into nicotinic acid but inefficiently: 1 molecule of nicotinic acid is synthesized from about 60 molecules of tryptophan. This synthetic route is the only means whereby a dietary deficiency of vitamin B₃ or a nicotinic acid dependency may be rectified, at least in part. The pellagra epidemic in the USA in the pre-1940s (brought on by the then vitamin B₃-deficient diet, particularly in the southern states) bears testimony to the limited redundancy expressed by the body's slight capacity to synthesize NAD.

The interface between NAD and the ETS is also a bottleneck because, although flavine adenine dinucleotide and glutathione can directly introduce electrons into the ETS (thus avoiding the NAD-ETS bottleneck), by doing so, they only account for about 15% of energy production, the rest being critically accounted for by electrons transferred by NAD.

When Hoffer described the effect of nicotinic acid in remitting schizophrenia and alcoholism,¹⁵ he attributed the improvement to a particular biochemical reaction: the preferential methylation of nicotinic acid in such a way as to inhibit the methylation of nor-epinephrine to produce epinephrine. Hoffer posited that the cause of schizophrenia is the accumulation of toxic oxidation products of epinephrine, particularly adrenochrome.

At the time that vitamin B₃ was thus proposed as a therapeutic methylation sink, it was not known that NAD provided such

an important key to the operation of the ETS, the key energy-producing component of the cell. With the benefit of that more recent knowledge, the implication for the cell when the NAD redox system fails is apparent, namely the accumulation of toxic oxidation products e.g. superoxide and also diminished energy currency (ATP). Thus, a better explanation for the key role of vitamin B₃ in preventing oxidative damage and sustaining cellular energy is accounted for by the fact that vitamin B₃ is a key precursor of NAD (the "N" of NAD=nicotinamide, solely derived from nicotinic acid). Turning again to oxidative stress in schizophrenia, recurrent depression and autism, diminished superoxide dismutase activity has been described in all three conditions.¹⁶⁻¹⁸ Figure 1 (p. 56) illustrates the key role of superoxide dismutase in disposing of the potentially toxic superoxide radical. The oxidative stress described in these conditions may, at least in part, be due to deficiency of superoxide dismutase activity.

Catalase activity has been reported to be diminished in alcoholics¹³ but whether catalase deficiency contributes to the cause of alcoholism or whether it is a result (or both), is unclear. In the past, this diminution of catalase activity has been ascribed to the result of alcoholism and not to a contributory cause. This interpretation of diminished catalase activity in alcoholics as an alcohol effect is understandable, considering the various biochemical effects of alcohol toxicity. However, the view that catalase deficiency is a result rather than a potential contributory cause of alcoholism was expressed before the time that: (1) the frequency of substance abuse and addictive behaviour was recognized to occur in about 50% of schizophrenics (indicating a potential link between the biochemical etiology of schizophrenia and alcoholism); (2) oxidative stress was widely recognized in schizophrenia and depression, with which alcoholism is genetically related; (3) experimental work with the C57BL/6J strain of inbred mice, characterized by slight catalase activity, showed them to have high levels of voluntary ethanol consumption

In view of the clinical and genetic links

between schizophrenia and alcoholism and the oxidative stress recognized in schizophrenia and depression, it is reasonable to propose that catalase deficiency is a contributory cause of alcoholism, rather than a result and that this deficiency at least contributes to oxidative stress associated with and possibly predisposing to alcoholism.¹³

As stated, nicotinic acid provides part of the NAD molecule and that molecule sits at a biochemical bottleneck. As such, the introduction of electrons by NAD into the ETS is a potentially rate-limiting step, if the dietary source of nicotinic acid is deficient or if there is nicotinic acid dependency. In such cases, the availability of nicotinic acid therefore determines: How well energy production by the ETS proceeds; how well the elimination of superoxide and hydrogen peroxide is effected; and which in turn determines how readily the potentially toxic products of oxidation are contained. It follows that an abundant supply of nicotinic acid tends to relieve oxidative stress and a deficiency to exacerbate it. In other words, the reported benefit of the use of nicotinic acid in schizophrenia is supported by the recent recognition of the underlying oxidative stress in this condition, the role of NAD at the biochemical bottleneck in the oxidizing/energy producing process described and the limited redundancy in the process that determines adequate levels of nicotinic acid for NAD synthesis.

Turning to the reported catalase deficiency in alcoholics, the reported benefit attaching to treatment of alcoholism with nicotinic acid appears to be due to the same mechanism by which NAD has the potential to eliminate oxidative stress in schizophrenia. However, dietary deficiency of a range of nutrients is a well-known result of alcoholism. Thus, according to this view, the use of nicotinic acid in the treatment alcoholism addresses both the cause and result of the condition.

The genetics of schizophrenia are illustrated by the family distribution of this disorder, for example there is a 13% chance of the occurrence of schizophrenia in the

children of a schizophrenic parent, and a 9% risk if the affected family member is a sibling.¹⁹ For a long time it was considered that the mother's defective mothering skills led to schizophrenia. Some years ago, an editorial in the *British Medical Journal* devoted to schizophrenia (this "puzzling" condition), described how the concept of the schizophrenogenic mother "dies hard." In fact if we look at the family distribution of schizophrenia through the lens of oxidative stress, we see how the personality of the mother may be determined by oxidative stress at the neurochemical level. It is easy to see that maternal schizotypic/neurotic behaviour (and therefore sub-optimal mothering skills) is a dependent variable determined by the status of her available biochemical strategies for overcoming oxidative stress: SOD, glutathione reductase and oxidase, catalase activities, and NAD status.

Turning to Hoffer's studies examining the effect of nicotinic acid in remitting symptoms of schizophrenia and alcoholism, he understandably confined his studies mainly to cases of schizophrenia and alcoholism attending his specialist psychiatric clinic. These cases are referred here to as: Index Cases. What he did not explore to the same extent was more epidemiologically-based research targeted at family members of those index cases referred to his clinic.

In view of the genetics of schizophrenia, it is not surprising that family members of index cases display traits of schizophrenia (Schizotypy). Thus, it is possible for individuals to display distressing clinical features such as exaggerated mood lability and a tendency to consume alcohol excessively, but not to the extent such as to trigger permanent lifestyle disaster.²⁰

Such features may be simply classified as follows:

1. No obvious schizoid traits apparent either to family members or work colleagues but possibly identifiable by psychiatrists.

2. Schizotypy traits displayed to family members or work colleagues and readily identified by specialist psychiatric assessment but traits of not such a degree as to

impact critically on relationships or work performance but possibly sufficient to render these sub optimal.

3. Florid but transient psychosis or alcoholism sufficient to critically affect relationships and workplace performance.

The question is therefore posed: Is there a role for nicotinic acid supplementation in family members of schizophrenics who display schizotypy (non-critical features of schizophrenia, such as episodic depression and excess alcohol consumption) sufficient to impair relationships or workplace performance, but not to the extent necessarily to trigger breakdown in both these areas and lead to psychiatric referral?

This question is considered in the following case history.

Case Presentation

The case involved a 45 year-old, intelligent Caucasian male running a successful business that he had started with colleagues (from student days) in a major city. His father was a chronic alcoholic who, at the age of 48 years was divorced from his wife at the time when his business failed. At that time, the son was aged 16 years. The son stayed in the father's home and, perhaps surprisingly, against the background of unfavourable home circumstances, graduated from university, and became an academic before starting his commercial enterprise, marrying and starting a family. On the surface, the son was managing his life well. However, by the age of 44 years, every week he was consuming over 50 units of alcohol (i.e. about 500 mL of pure alcohol consumed from alcoholic beverages) and experiencing episodes of depression. His episodes of depression were distressing but not severe enough, initially, to critically interfere with the running of his business, to interfere critically with family life or to prompt a medical consultation. This unstable equilibrium continued for about ten years and then came to a head in the following manner. He applied for life insurance but his application was rejected because of the result of the medical examination that comprised part of the application

process. Specifically, the result of his blood tests showed that his serum cholesterol was above the permitted level. He did not wish to use statins to address this, so started taking nicotinic acid, initially at a dose of 50 mg per day and slowly increasing from there. He achieved a target dose of nicotinic acid 500 mg twice daily. His cholesterol reached an acceptable level for the purpose of his life insurance application but what was unexpected and gratifying were the other changes. His episodes of depression remitted and his alcohol consumption diminished effortlessly from 50 units per week to 7 units per week (i.e. about 70 mL of pure alcohol from alcoholic beverages).

Could this be a factitious result? He started his nicotinic acid supplementation in the third quarter of the year and his improvement persisted throughout the winter. Accordingly his mood could not have been positively affected by increased exposure to solar radiation, according to the pattern of change seen with seasonal affective disorder. Additionally, his improvement cannot readily be attributed to a placebo effect because the rationale of using nicotinic acid was to diminish his cholesterol level and not to seek improvement in his depressive episodes and diet, which was quite unexpected.

Conclusion

Schizotypy features are found about four times more commonly in relatives of schizophrenics, compared to the occurrence rate in the general population. It is proposed that nicotinic acid is useful in remitting disabling schizotypy features as well as in the treatment of schizophrenia.

Competing Interests

The author declares that he has no competing interests.

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