

Negative Symptoms, Glutathione Peroxidase, and Dopamine Receptors

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Abstract

An environmental insult in conjunction with low levels of glutathione peroxidase might be associated with a form of schizophrenia. This double insult could result in the dysregulation of a dopaminergic system. Hypersensitive autoreceptors and up-regulated postsynaptic D2 receptors might be a consequence. Cells down the line from dopamine neurons might burst abnormally on a daily basis in patients who present with both positive and negative symptoms. Both hypo- and hyper- dopaminergic activity in a single neuronal system might be present in these patients, and in behavioral terms things need not even out. These theoretical considerations have possible treatment ramifications. Levodopa, dopamine autoreceptor antagonists, and selenium, may have a role in the treatment of various schizophrenic sub-populations.

What follows is a theoretical paper — it establishes nothing indubitably. This paper is intended to be suggestive.

Glutathione Peroxidase

Research indicates that low levels of the enzyme glutathione peroxidase are in evidence in various schizophrenic populations (Abdalla et al., 1986; Buckman et al., 1987; Buckman et al., 1990). Buckman et al. (1987, 1990), claims that low levels of this enzyme are associated with negative symptoms and brain damage.

A low level of the enzyme glutathione peroxidase is itself not a marker for schizophrenia. Many individuals with low levels of glutathione peroxidase are not schizophrenic (Valentine et al., 1989, p. 2352). Buckman et al. (1990), theorizes that an environmental insult to the brain and low levels of the enzyme both contribute to the disease. Buckman et al. (1990), argues that a genetically determined low glutathione peroxidase level is a

"vulnerability factor" for schizophrenia.

Glutathione peroxidase is an antioxidant enzyme. This enzyme catalyzes the hydrogen peroxide—reduced glutathione reaction. The end products of this reaction are water and oxidized glutathione (Mehler, 1986, p. 483).

Here, it is suggested that low levels of glutathione peroxidase, no matter what the cause, might be a "vulnerability factor" for the development of a form of schizophrenia, and too, that pharmacological treatments that increase glutathione peroxidase levels may have a role in the treatment of this form of schizophrenia, in which negative symptoms and brain damage are in evidence.

Glutathione peroxidase is under both genetic and environmental control. The human gene for glutathione peroxidase has recently been isolated and it is located on chromosome 3 at region 3q11-13.2 (Chada et al., 1990). Levels of glutathione peroxidase are additionally affected by selenium levels. Glutathione peroxidase levels are decreased in individuals with low selenium levels. Glutathione peroxidase levels increase as selenium levels increase up to a saturation point (Rea et al., 1979; Lane et al., 1981; Gromadzinska et al., 1988; Whanger et al., 1988; Lockitch, 1989; Lloyd et al., 1989). A linear correlation has been observed between whole blood selenium concentrations and blood glutathione peroxidase activity up to blood selenium concentrations of .100 g/ml. Above these concentrations the enzyme activity tends to plateau (Thomson et al., 1977).

At this point I will note an additional reason for believing that selenium and the enzyme glutathione peroxidase may be involved in the etiology of schizophrenia. Research indicates that states in which relatively little selenium is passing through the food chain have high incidences of schizophrenia (Foster, 1988). Likewise, countries known to be deficient in selenium have high incidences of schizophrenia. Norwegians and Swedes are known to be extremely deficient in the intake of selenium

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and Norway and Sweden both have high incidences of schizophrenia (Foster, 1990). Conversely, nations with a low incidence of schizophrenia seem to have high selenium intakes. Witness Japan.

If low levels of glutathione peroxidase are implicated in the disease then the genetics of the disease might be somewhat complicated. Some individuals with the disease will have defective glutathione peroxidase genes, but others will not. Things might go something like this. What follows must be viewed as extremely tentative.

Defective gene + no environmental insult to brain = no disease. Functional gene + low levels of selenium + no environmental insult = no disease. Functional gene + environmental insult = no disease. Defective gene + environmental insult = a form of schizophrenia. Functional gene + low levels of selenium + environmental insult = a form of schizophrenia.

Conceivably, however, an environmental insult of sufficient magnitude might even in the presence of normal levels of glutathione peroxidase be enough to trigger the disease. The reverse, however, is not true — a low glutathione peroxidase level will, in and of itself, not trigger the disease.

What form might the environmental insult take? Possibly the environmental insult might be of viral origin. Keshan Disease, a cardiomyopathy, is a disease associated with low levels of selenium. Various researchers believe that low selenium levels are necessary for the development of the disease but not sufficient. Some researchers of Keshan Disease hypothesize that low selenium levels might make people susceptible to a viral infection (Gu and Cheng, 1986). Keshan Disease is totally preventable by selenium supplementation.

Individuals can have low levels of selenium in the blood for various reasons — not merely because their diet is low in selenium. Selenium antagonists exist. For example zinc is thought to be a selenium antagonist. Too, a new selenium containing protein has recently been isolated in rat plasma. This protein, Selenoprotein P, is thought to possess a transport function (Motsenbocker and Tappel, 1982; Burk, 1989). Might a problem at this juncture, with this particular protein, possibly result in low levels of the enzyme glutathione peroxidase?

I might point out here that selected individuals might have problems absorbing selenium for various reasons. A protein, any protein, that affects selenium levels might then have a role to play in the etiology of a form of schizophrenia. If selenium levels are affected by levels of a protein then conceivably the gene for that particular protein might be involved in the etiology of this form of schizophrenia. From a purely theoretical standpoint the glutathione peroxidase gene need not be the only relevant gene. I emphasize that these are purely theoretical considerations — this paper is intended to be suggestive. Apparently, selenium has various functions — antioxidant and otherwise — above and beyond its regulation of glutathione peroxidase, and it is possible that schizophrenics who have low glutathione peroxidase levels due to a low selenium level might present with a different clinical picture than do schizophrenics who have low glutathione peroxidase levels for some other reason — for example a defective glutathione peroxidase gene.

As mentioned glutathione peroxidase is an antioxidant enzyme. How might this be relevant to the etiology of schizophrenia? Individuals who have researched Parkinson's disease theorize that dopaminergic systems might be prone to damage by free radicals (Halliwell, 1989). L-deprenyl is now being used by various clinicians to delay the onset of Parkinson's disease. It is argued that L-deprenyl is effective in delaying the onset of Parkinson's disease because it prevents the formation of free radicals that can damage dopaminergic neurons (The Parkinson Study Group, 1989; Tetrud and Langston, 1989). This supposition is currently a matter of some controversy.

Some researchers argue that free radicals may play a part in the etiology of tardive dyskinesia, as they might damage neuronal systems. Vitamin E, an antioxidant, has been partially effective in the treatment of tardive dyskinesia (Lohr et al., 1988; Elkashef et al., 1990). Researchers have additionally argued that free radicals may be involved in schizophrenic burnout (Cadet et al., 1987).

Possibly, then, low levels of glutathione peroxidase in association with a brain trauma in an appropriate part of the brain might have long term adverse effects on dopaminergic neurons and a subtype of schizophrenia might

be a consequence in which brain damage and negative symptoms are much in evidence.

Dopamine Receptors

Assuming free radicals adversely affect dopamine receptors what form might the damage take? The following is a possible scenario.

If we assume for some reason that dopaminergic autoreceptors become hypersensitive then the release of dopamine and the synthesis of dopamine ought to be inhibited (Cooper et al, 1986, p. 279). Too little dopamine will enter the synaptic cleft, and by way of compensation might not post-synaptic dopaminergic receptors up-regulate? I suggest that they might. An individual with hypersensitive dopaminergic autoreceptors and up-regulated post-synaptic D2 receptors might have the bad fortune to be afflicted with both positive and negative symptoms. Wide gyrations in physiological tone might occur in a single neuronal system within fairly short time periods. How might this come about?

The individual's hypersensitive autoreceptors result in a decrease in the synthesis and release of dopamine with consequent negative symptoms, but the afflicted individual's dopaminergic system from time to time over-compensates and high levels of dopamine are synthesized — dopamine will hit up-regulated postsynaptic D2 receptors and an excessive physiological reaction will follow, i.e. positive symptoms ensue. This scenario suggests that despite over all low levels of dopamine, from time to time, the system over-compensates and in a surge dopamine is synthesized and released. Periodically, then up-regulated post-synaptic receptors are inundated by dopamine and positive symptoms result despite the underlying hypo-dopaminergic tone. I suggest a type of on-off phenomenon is present in patients who present with both positive and negative symptoms. Parkinson's patients document the fact that on-off phenomenon are quite possible in patients with damaged dopaminergic neuronal systems. This scenario does intimate that in this patient population dopamine levels do not remain high for long periods of time. In sum the individual can not avoid several biological catastrophes a day. (This scenario seems reasonable, but, of course, reasonable scenarios are not necessarily true scenarios.) Various researchers argue that D2 receptors

are increased in schizophrenia (Seeman et al., 1987; Pearce et al., 1990). The present article suggests a reason for this increase — postsynaptic D2 receptors are increased due to a decrease in the synthesis and release of dopamine, and autoreceptors are hypersensitive as a consequence of an environmental insult—free radical assault. Autoreceptors as well as post-synaptic D2 receptors might function inappropriately in some forms of schizophrenia.

What might happen as a consequence of the dysregulation of dopaminergic D2 receptors? Cells that follow dopamine neurons will burst inappropriately many times a day. Dopamine is generally deemed an inhibitory neurotransmitter. When dopamine is applied to single neurons firing rates are decreased (Cooper et al., 1986, p. 252). When — at odd intervals — up-regulated post-synaptic D2 receptors become bound by dopamine, cells that follow dopamine cells become relatively depressed. (Nonetheless, in behavioral terms this will show itself as a kind of 'excitement'.) But as a rule, too little dopamine is in the synaptic cleft, and consequently cells down the line from dopamine cells burst inappropriately. Why? These cells are not appropriately inhibited. (In gross terms, this ought to work its way up as a kind of profound behavioral energy.) The point here is that cells down the line from dopamine cells ought to burst inappropriately several times a day if autoreceptors are hypersensitive and post-synaptic D2 receptors up-regulate as a consequence.

One caveat. I do not here suggest that the scenario outlined above is absolutely stable.

Briefly, hypersensitive autoreceptors result in a decrease in the synthesis and release of dopamine, and in response post-synaptic D2 receptors up-regulate. Dopaminergic tone is basically depressed but the system overcompensates several times a day and up-regulated post-synaptic receptors can then be bound by dopamine. Things don't even out in behavioral terms.

Schizophrenia is a disease that exists in time, and over time as receptors adapt, scenarios must be modified. The above scenario is an attempt to tie biology to a clinical reality. Patients do present with both positive and negative symptoms, and possibly a combination of hypersensitive autoreceptors and up-regulated post-synaptic D2 receptors might

explain the combination of symptoms. Patients who present with schizophrenic burnout and patients that present with only positive symptoms are not intended to be covered by the above scenario. Some patients might never exhibit positive symptoms. Why? Possibly they do not experience surges in the synthesis and release of dopamine.

Implications

This theory has several implications.

One. Pure dopamine autoreceptors agonists ought to, minimally, worsen negative symptoms. Possibly dopamine autoreceptors agonists might be of some use in the patient who happens to be exclusively afflicted by positive symptoms but in no one else.

Autoreceptors antagonists, on the other hand, ought to have some role in the treatment of schizophrenia. Sulpiride and pimozide are thought by some to preferentially antagonize pre-synaptic receptors at low doses (Puech et al., 1978; Costall et al., 1980). (A question does exist as to whether pimozide actually does antagonize pre-synaptic receptors at low doses. However, regardless of its mode of action low doses of pimozide do seem to block the actions of low doses of apomorphine on pre-synaptic receptors, and this might be the relevant point.) This would increase the synthesis and release of dopamine. As previously noted pimozide has been used successfully in the treatment of negative symptoms (Falloon et al., 1978; Meltzer et al., 1986; van Kammen et al., 1987; Feinberg et al., 1988). Sulpiride, too, has been successfully used in the treatment of negative symptoms (Elizur and Davidson, 1975; Petit et al., 1987). Sulpiride and pimozide might additionally occupy the autoreceptor and prevent the autoreceptor's agonization by dopamine. Tecott et al. (1986), indicates that pimozide down-regulates dopaminergic D2 binding sites. This conceivably might be significant. Levodopa, too, might play a role in the treatment of schizophrenia. Hypersensitive autoreceptors should decrease the synthesis and release of dopamine and levodopa might correct this imbalance. Levodopa has successfully been used to treat negative symptoms (Gerlach and Lohdoff, 1975; Ogura et al., 1976).

Two. Investigators might well spend time examining those portions of the brain in which dopaminergic autoreceptors are in evidence.

Most dopaminergic systems have autoreceptors, but some do not (Cooper et al., 1986, p. 282). If the outlined theory is correct, that portion of the brain relevant to at least one form of schizophrenia ought to be a portion of the brain in which autoreceptors are in evidence. I suggest the burden of proof be shifted onto researchers who believe that all dopaminergic autoreceptors function in a completely normal mode in schizophrenia. Sufficient reason does not exist for the belief that all autoreceptors retain an ability to function normally in individuals afflicted with this disease.

Three. In individuals with low glutathione peroxidase levels consequent to a low selenium level, supplemental selenium ought to be helpful. This idea is readily testable. If glutathione peroxidase levels are low because selenium levels are low it might be appropriate to address the root cause of the low selenium level.

Four. Antioxidants might be useful in the treatment of the disease. Research suggests that antioxidants can increase the absorption of selenium. Vitamin E, vitamin A, ascorbic acid, and synthetic antioxidants can increase the bioavailability of selenium (Combs and Combs, 1986, pp. 156-172). However, increased bioavailability possibly entails that the selenium supplement and antioxidant be taken together with food.

Five. The theory outlined, additionally, suggests that the incidence of schizophrenia ought to be increased in that portion of the population which has a defective glutathione peroxidase gene, but it must be remembered that it is not suggested here that a low glutathione peroxidase level, in and of itself, causes schizophrenia. The site of the glutathione peroxidase gene has recently been determined. The human gene for glutathione peroxidase has been isolated and it is located on chromosome 3 at region 3q11 -13.1 (Chada et al., 1990).

Why are the current generation of neuroleptics effective at all in this sub-population of patients? The theory implies that these drugs are successful because they address the problem of up-regulated post-synaptic D2 receptors. The theory outlined above additionally implies that these drugs are not more successful because they do not address the problem of hypersensitive autoreceptors, and,

that these drugs do not address the original shock which might be best viewed as a function of an environmental insult (a virus?) and oxidative damage.

Six. Possibly animal models of this subtype of schizophrenia might be created in light of this theory. Powerful specific autoreceptor agonists (in selenium deficient animals?) might be used to induce a form of schizophrenia in experimental animals. Dopaminergic autoreceptor agonists might bear the same relationship to this sub-type of schizophrenia as amphetamine does to paranoid schizophrenia.

Personal Note

I am a diagnosed schizophrenic. I take 1250 milligrams of levodopa, 200 milligrams of carbidopa, 2 milligrams of pimozide, and an extremely broad range of antioxidants with a heavy emphasis on selenium — 550 micrograms. I always take my selenium with food, but as of yet I have not been able to raise my selenium blood level above .100 g/ml.

My intake of antioxidants tends to vary, but I currently take 7000 milligrams of Vitamin C, 800 International Units of Vitamin E, 60 milligrams of Coenzyme Q10, 50,000 International Units of Beta Carotene, 200 milligrams of riboflavin, and 1000 milligrams of bioflavonoids a day. In addition to these antioxidants I take 1000 mcg. of Vitamin B¹², 800 mcg. of folic acid, 100 milligrams of Vitamin B¹, 500 milligrams of pantothenic acid, and 1300 milligrams of calcium with added Vitamin D — 250 International Units. I take one additional vitamin that requires a note. I take 50 milligrams of Vitamin B⁶ when I take my next to last dose of Sinemet — I surmise at these times that my carbidopa level will be relatively high. (Some research indicates that B⁶ potentiates levodopa when it, levodopa, and carbidopa are taken together, and this is my anecdotal experience.)

I do not suggest that the program outlined above is an optimal program.

Conclusion

An environmental insult in conjunction with low levels of glutathione peroxidase might be associated with a form of schizophrenia. This double insult could result in the dysregulation of a dopaminergic system. Hypersensitive autoreceptors and up-regulated post-synaptic D2 receptors might be a consequence. Cells down the line from dopamine neurons burst abnormally on a daily basis and the patient presents with both positive and negative symptoms. A kind of on-off phenomenon is present in these individuals. In behavioral terms things do not even out. The theory has treatment implications.

Heretofore, this form of the disease has not been well treated, but if my own experience is an appropriate measure much more can be done than is now being done for these patients.

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