BIOMARKERS AND CAUSATIVE FACTORS OF SCHIZOPHRENIA

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ABSTRACT

Schizophrenia is a major debilitating, complex and costly illness that strikes 1% of the world's population. It is found in every society from the most primitive to the largest and most technologically advanced society. The excessive degree of cigarette smoking exhibited by schizophrenic patients suggests that they might be self-medicating to ameliorate to some extent the characteristic positive, negative and cognitive symptoms associated with the disease. Morphological examinations found alterations in nicotinic receptors in postmortem tissue from schizophrenic individuals compared to controls, especially in the $\alpha 7$ and $\alpha 4\beta 2$ subtypes. These results have spurred the development of new pharmaceuticals specifically designed to modulate nicotinic receptor function. The initial results from clinical trials of these new drugs appear promising, potentially opening new avenues of treatment for this devastating disease. In the present review article, the authors have described various neuromodulators such as Dopamine, Glutamate, Acetylcholine, Serotonin, GABA etc. responsible for causing schizophrenia.

Keywords: Schizophrenia, Neuromodulators, Glutamate, Dopamine, Solitude.

INTRODUCTION

Schizophrenia is a complex illness affecting roughly 1% of the world's inhabitants¹. The risk of developing schizophrenia is almost equal in men and women², but gender differences do exist in the initial age of onset of the disease. First hospital admissions peak in the early twenties in young men, but not until the late twenties in young women, although women exhibit a second smaller peak in initial admissions after age 45. Schizophrenia is a very costly disease. Treatment of psychotic disorders worldwide³ accounted for 1.5 – 3.0% of national health expenditures (United Kingdom 1.5 – 3.0%, Germany - 1.3%, the Netherlands and France 2.0%, United States 2.5%). A greater understanding of the etiology of schizophrenia is, therefore, not only important from an individual standpoint, but also important for society as a whole.

Symptoms of Schizophrenia: Schizophrenia is characterized by three general types of symptoms: Positive symptoms (psychosis), Negative symptoms and Cognitive symptoms. Not all schizophrenic patients exhibit each of these symptoms, nor are these symptoms exclusive to schizophrenia. Positive symptoms refer to a loss of contact with reality and comprise of hallucinations, delusions, bizarre behavior and positive formal thought disorders. Negative symptoms refer to a diminution in or absence of normal behaviors and include flat affect, alogia, avolition and anhedonia. Cognitive symptoms manifest as deficits in attention, learning, memory, concentration and executive functions (abstract thinking, problem solving). Cognitive impairment appears to be present pre-morbidly in individuals that later develop schizophrenia, increases slightly just prior to the onset of psychotic symptoms and may show minimal further deterioration over the course of the disease, or may continue to worsen. Of the three symptom categories, degree of cognitive dysfunction appears to be the best predictor of functional outcome in schizophrenic patients and may, with appropriate cognitive assessment tools, serve as a vulnerability marker for schizophrenia. The resulting

disorganized thought and display of behaviors that do not meet with social expectations are often associated with the development of poor memory and a shortened attention span. The apparent decline in cognitive processing is often reflected in disorganized speech, further suggestive of a deficit in information processing. A decrease in emotional tone and of reaction to social and other external stimuli may parallel a decline in social functioning, emphasizing the importance of the integrity of higher cortical circuits in mediating receptive, productive and appropriate social interaction, or 'successful' human social 'behavior'.

Biomarkers/causative factors of Schizophrenia

- Dopamine
- Glutamate
- Acetylcholine
- Serotonin
- GABA
- Nor epinephrine
- Miswiring of the brain during development
- An inherited disorder exacerbated by stress and hormonal changes
- A transmissible viral infection
- Prenatal hypoxia
- Autoimmune damage
- A neurodegenerative disorder (such as Alzheimer's, Parkinson's)
- An inherited predisposition
- The loss of tissue due to neurotoxicity
- Social stressors in urban settings
- Depletion of certain fatty acids in cell membranes
- Dietary Exorphins from milk

A Diaspora of theories proposed for causing schizophrenia: A plethora of theories have arisen to explain the deficits associated with schizophrenia including specific or 'global' changes in neurotransmission involving a given neurotransmitter, cell type or receptor, and a host of changes

in brain function elicited by agents as diverse as stress, developmental aberrations, hormonal changes, steroids, solitude, and viral infection.

Dopamine as the “Wind of the Psychotic Fire”: The dopamine hypothesis of schizophrenia^{4,5} has comprised two distinct ideas: a dopamine hypothesis of antipsychotic action and a dopamine hypothesis of psychosis. The two are related but different. The dopamine hypothesis of antipsychotic medications can be traced to the early observation that antipsychotics increase the turnover of monoamines⁶, more specifically, dopamine⁷, and this observation anticipated the discovery of the “narcoleptic receptor”, now called the dopamine D2 receptor, providing a mechanistic basis for the dopamine hypothesis of antipsychotic action. A central role for D2 receptor occupancy in antipsychotic action is now well established, buttressed by neuroimaging studies using positron emission tomography and single photon emission computed tomography⁸. However, the importance of dopamine receptors in the treatment of psychosis does not by itself constitute proof of the involvement of dopamine in psychosis. Early evidence for a role of dopamine in psychosis was the observation that psychostimulant agents that trigger release of dopamine are associated with de novo psychosis⁹ and cause the worsening of psychotic symptoms in patients with partial remissions¹⁰. Further evidence came from postmortem studies that showed abnormalities in dopaminergic indexes in schizophrenia, although the interpretation of these data was always confounded by drug effects^{4,5}. The most compelling evidence in favor of the dopamine hypothesis emerges from neuroimaging studies (details reviewed in references¹¹). The central involvement of a deficit in dopamine function in schizophrenia is suggested by the observation that medications which alleviate the psychosis of schizophrenia such as chlorpromazine (Thorazine) act by antagonizing the actions of dopamine at its receptor, especially the D2 receptor. Bilder proposes that dopamine systems mediate the comparison of observed (perceived) and expected ('normal') patterns of events within resonant cortical circuits, measuring departures from 'normality' as deviations from patterns of expected resonance. By antagonizing dopamine receptors it is possible to block these perceived shifts, and the attendant projections of 'nonexistent' perceived events (hallucinations) during the active phase of schizophrenia. Dopamine receptors are present in the prefrontal cortex (PFC), nucleus accumbens, striatum, hypothalamus and hippocampus, and are believed to mediate the motivational aspects of reward and reinforcement following dopamine (DA) release from projections from the ventral tegmental area into the striatum, nucleus accumbens and PFC which are under hippocampal influence. Further, drugs which increase dopamine by blocking its reuptake by the DA transporter into nerve terminals such as cocaine and amphetamine cause the positive symptoms of schizophrenia, such as increased locomotion, hallucination and other aspects of psychosis at high concentration. As dopamine is held to modulate, or 'color', the tone of excitatory transmission through projections of the frontal and temporal cortex to the basal ganglia (e.g. striatum) and other areas, dopaminergic transmission is thought to be implicated in the deficit in information processing associated with the prefrontal cortex, the PFC having one of the highest concentrations of dopaminergic nerve terminals. It is believed that a high concentration of certain DA receptors interact with glutamate receptors to facilitate memory formation in the PFC (D1?).

Professor Goldman-Rakic has argued that the 'derailed' train of thought associated with schizophrenia is due to a deficit in working memory, the executive function of the prefrontal cortex. As the prefrontal areas receive a high concentration of dopamine, and drugs that are effective in treating schizophrenia act on these dopamine receptors, such as clozapine, Professor Goldman-Rakic argues that enhanced dopamine levels 'induced' by clozapine act to improve thinking and memory. Perhaps this is the mechanism by which cocaine and ritalin (methylphenidate) enhance cognitive performance, attention and memory, by increasing availability of DA in the PFC through an inhibition of reuptake. If so, there must be a fine balance, as cocaine and other dopamine uptake inhibitors also cause the positive symptoms of schizophrenia at high doses.

The Glutamate Hypothesis: Kim et al.¹² reported reduced concentrations of glutamate in the CSF of patients with schizophrenia and first proposed that decreased glutamatergic activity may be an etiologic factor in the disorder. This finding was replicated by some¹³ but not all subsequent studies¹⁴. In addition, the concentration of *N*-acetyl-aspartyl glutamate (NAAG), an acidic dipeptide that acts as an antagonist at NMDA receptors¹⁵ was increased in the hippocampus, and the activity of glutamate carboxypeptidase II (GCP II), the enzyme that cleaves NAAG to produce glutamate and *N* acetyl aspartate (NAA), was selectively reduced in the frontal cortex, temporal cortex, and hippocampus in the schizophrenia brains. Much of the transmission of excitatory information in the brain occurs via the binding of glutamate to its receptors, and, directly or indirectly, the activity of most neurons in the brain is influenced by this excitatory amino acid. The blockade of one specific glutamate receptor, the NMDA receptor, which plays a critical role in the plasticity of nervous connections associated with learning and memory, appears to mimic certain symptoms of schizophrenia. Two of the more popular psychoactive drugs of the 1970's, phencyclidine ('Angel Dust') and ketamine ('Special K') specifically block NMDA receptors and cause hallucinations in humans, as well as stereotyped, repetitive behavior and social withdrawal in both rats and humans, thereby reproducing both the positive and negative symptoms present in schizophrenia. Ketamine, a dissociative anesthetic, causes a schizophrenia-like psychosis in healthy individuals and exacerbates the psychotic symptoms in schizophrenic patients, decreasing their apparent responsivity to environmental stimuli. In light of these observations, one theory which has been put forward is that schizophrenia results from a hypoactivity of glutamatergic transmission in the brain. A decrease in glutamatergic output from the hippocampus, coupled with the high levels of glutamate receptors present (particularly NMDA) in the anterior cingulate cortex, one of the principal targets of hippocampal glutamatergic output, may underlie some of the diminished cognitive aspects and processing deficits associated with schizophrenia. Memory and other cognitive deficits in schizophrenic patients may be explained in part by reductions in transcript (mRNA) for the glutamate receptor subunits NMDAR1, GluR1, GluR7 and KA1 mRNA levels in frontal cortex both in drug-free and drug-withdrawn schizophrenics. The NMDA receptor has a key function in information processing as a coincidence detector implicated in the molecular basis of learning and memory, as converging and coincident signals must be received by a nerve cell bearing this receptor upon its receiving terminals, or

dendrites, for its activation. Many have proposed that abnormalities in the functioning or expression of this receptor may underlie both a predisposition to and a manifestation of schizophrenia. Indeed mice genetically engineered to have a reduced level (5%) of NMDA receptor expression display social and sexual impairments in their interactions in addition to the stereotyped behaviors and increased motor activity of schizophrenia, which could be ameliorated by antipsychotic drugs that antagonize both dopamine and serotonin receptors. In the social interaction test, an animal model of schizophrenia, PCP (a non-competitive NMDA antagonist) induces social isolation and stereotyped behavior in rats which could also be overcome by anti-psychotic drugs which act at DA receptors. Indeed, a measurable disturbance in glutamate and N-acetyl aspartic acid levels has been shown in un-medicated schizophrenic patients.

The Acetylcholine Hypothesis: This hypothesis proposes that the excessive smoking observed in schizophrenic patients occurs, because both, the need to smoke and the vulnerability to schizophrenia arise from a common neurobiological substrate¹⁶. Support for this viewpoint is provided by reports showing that the initiation of smoking often precedes the onset of schizophrenic symptoms¹⁷. Nicotine has been demonstrated to increase the release of dopamine, particularly in the mesocorticolimbic and nigrostriatal pathways¹⁸. The nicotine-induced increase in dopaminergic tone supports the notion that smoking may alleviate anhedonia and Parkinson's like symptoms produced by dopaminergic blockade, a component of the typical and many of the atypical antipsychotics¹⁹. Alternately, the nicotine in cigarette smoke may relieve symptoms unaddressed by antipsychotic medications, such as cognitive impairments or sensory processing deficits. Cognitive issues are now a recognized component of the schizophrenia symptom constellation and are receiving as much attention as positive and negative symptoms²⁰. Improvement in cognition in schizophrenic patients has been positively correlated with improved functional outcomes²¹. Several studies have demonstrated that stimulation of nicotinic acetylcholine receptors (nAChR) either by nicotine²² or through cholinomimetics such as physostigmine²³ produces improvement in cognitive function in schizophrenic patients. It is notable that the prevalence of smoking amongst schizophrenics is 3 times higher than in the general U.S. population (20-25%), as over 75% of schizophrenics smoke. Further, nicotine withdrawal may temporarily worsen schizophrenic symptoms, suggesting that nicotine may help to control psychotic symptoms. The specificity of nicotine in its action upon a subtype of 'fast' acetylcholine receptors, known for their mediation of rapid excitatory signals, especially within the presynaptic terminal, infers a central role for acetylcholine in the etiology of schizophrenia. Cortical acetylcholine is known to mediate the detection, selection and processing of stimuli and associations, and may additionally play a role in the filtering and allocation of other processing resources for these attentional functions. Attention is impaired if increases in cholinergic tone are blocked either by increasing GABAergic activity or by removing cholinergic inputs. Nicotine modulates both the failure to see inhibition of the P50 auditory-evoked response to repeated stimuli and the dysfunction in smooth pursuit eye movement associated with schizophrenia. Indeed D2 (and D1) antagonists attenuate increases in cortical ACh release stimulated by dopamine release within the Nucleus

Accumbens. As DA release is elevated in the Nucleus Accumbens during both the acute phase of schizophrenia and as a result of the action of psychoactive drugs, it is suspected that cholinergic tone in the forebrain is altered in schizophrenia. Further this opens up the possibility of using nicotine as a treatment in schizophrenia, as it exhibits anxiolytic, attentional and cognitive benefits. Is schizophrenia attributable in part to a hypo cholinergic deficit? However, just as 'fast' nicotinic receptors may be implicated in schizophrenia, so may 'slow' acetylcholine receptors, inferred by the actions of clozapine, which has a high affinity for these slow 'metabotropic' ACh receptors. This raises the possibility that the functional deficits in schizophrenia are attributable to changes in function of slow as well as fast receptors.

The Serotonin Hypothesis: Elevated levels of serotonin (5-HT) are found in schizophrenia, and SSRIs are alleged to have created an epidemic of suicide attempts. Another potent serotonin-releasing agent, MDMA, otherwise known as ecstasy, causes hallucinations, memory deficits and other psychiatric symptoms affecting mood, cognition and anxiety which are related to changes in serotonergic function. 5-HT_{2A} receptor regulation appears essential for many of the features of the atypical antipsychotic drugs as described previously by Meltzer²⁴. All approved and clinically available atypical antipsychotic drugs have a favorable 5-HT_{2A}/D₂ affinity ratio in vitro and in vivo. However, 5-HT_{2A} antagonism alone is likely to be ineffective, as seen, for example, in MDL100907. The 5-HT_{2B} receptor is likely an anorectic agent. 5-HT_{2C} receptor antagonists are likely to produce weight gain and possibly seizures and the 5-HT_{2C} agonists are likely to be anorectic²⁵. Thus, weight gain due to atypical antipsychotic drugs might be due to 5-HT_{2C} blockade. The 5-HT_{2A} receptors are found on apical dendrites and dendritic spines of pyramidal neurons in both the rat and primate cortex. The action of clozapine, an atypical antipsychotic used in the treatment of individuals resistant to dopamine antagonists, which is noted to have a high affinity for serotonin receptors, suggested that serotonin (5-HT) may also play a role in the etiology of schizophrenia. Prozac (fluoxetine), anti-depressant, as well as other serotonin reuptake blockers (SSRIs), are alleged to cause long-term deficits in memory, concentration and even mental disability, disrupting perceptions of reality and creating false memories.

The GABA hypothesis: Disputes have arisen as to whether GABA receptor function is altered in schizophrenics from evidence obtained from binding studies although GABAergic projections are certainly involved in mediating the effects of dopamine released from the nucleus accumbens upon activity in the prefrontal cortex. Benzodiazepines, which act to increase the efficacy of transmission through GABA receptors and which are used both as sedatives and in the treatment of anxiety, have also been shown to ameliorate the core positive symptoms of schizophrenia. Indeed the brains of cocaine addicts, who exhibit schizophrenic symptoms, are more sensitive to benzodiazepines than those of drug-free individuals, indicating a change in GABA pathways in these individuals. GABA receptors have further been shown to be important in the acquisition of behavioral sensitization to drugs that induce schizophrenia-like behaviors, such as methamphetamine. The temporolimbic hypothesis suggests two phases, a first in which a preferential loss of GABA

receptors bearing NMDA glutamate receptors occurs, making the brain effectively hypo functional for NMDA receptors, and a second stage in which the neural circuits altered by the loss of these GABAergic neurons are activated in late adolescence, but are consequently dysfunctional. Recent interest has focused upon the reelin gene (RELN), whose expression is decreased by 50% in the telencephalic GABAergic interneurons of the PFC, temporal cortex, and hippocampus & also the glutamatergic cerebellar granule cells in schizophrenic patients. Reelin's signaling target, DAB1, is present in the neuropil of hippocampal & prefrontal cortical pyramidal neurons as well as that of cerebellar Purkinje neurons. Further a second generation of telencephalic (including PFC, temporal cortex & hippocampus) region RELN is expressed in the adult cortex by horizontal and bitufted GABAergic interneurons, and thus RELN mediated signaling, similar to that which is operational during development, may continue during adult neurogenesis. Further there are alterations in the level of GAD expression in GABAergic neurons in the PFC and changes in GABA-A receptor density in the dentate gyrus and corticolimbic structures in schizophrenic patients.

The anatomical and developmental theory of schizophrenia: A developmental miswiring of dopaminergic inputs onto GABAergic neurons in the cortex probably occurs around birth. Since the cortical dopamine system continues to mature until adolescence, the formation of misplaced connections during the normal ingrowth of dopaminergic fibers which occurs at this time, possibly exacerbated by stress, could trigger the onset of symptoms. Further evidence for a developmental onset comes from studies with rhesus monkeys irradiated with X-rays during fetal development which resulted in no ill effects until puberty, when schizophrenia-like symptoms such as poor working memory and hallucinations began to emerge. This lends further weight to the theory that fetal brain damage predisposes an individual to the onset of schizophrenia at puberty. The diverse symptoms of schizophrenia are in fact attributable to a single disorder linked by a neurodevelopmental mechanism that results in the misconnection of neural circuitry, and specifically within the cortical-thalamic-cerebellar-cortical (CCTCC) circuit which is critical in the synchronous firing of neuronal centers involved in the smooth co-ordination of mental processes. When the synchrony of the CCTCC circuit is impaired, the patient suffers from cognitive dysmetria, and this impairment of basic cognitive processes defines the hallmark of schizophrenia. Neuropathological changes occurring during the developmental stages of formation of the hippocampus has become a popular theory in predisposing an individual to schizophrenia, as the hippocampus is central in the processing, routing and filtering of sensory information which are known to be affected in schizophrenia. A loss of inhibitory neurons (GABA) appears to occur within the limbic lobe during development, concomitant with an infiltration of processes from excitatory neurons from elsewhere in the cortex, possibly predisposing to excitotoxicity. It seems that losses of neurons (gray matter) are reported to occur in schizophrenia by many groups, especially from the hippocampus, the amygdala, the superior temporal gyrus, parahippocampal gyrus and thalamus and the PFC has been reported to decrease in volume in some patients. However, a significant proportion of individuals diagnosed as schizophrenic do not show symptoms until very

late in life, seeming to argue against an exclusively developmental basis for schizophrenia. It may, however, be the case that the estimated 5% decrease in the volume of gray matter in the cortex may be due to a decrease in the number of connections between cells, including dendrites and chandelier axon cartridges, rather than primarily due to the loss of neurons or glia. Thus the poverty of thought, attention and memory associated with schizophrenia may reflect a poverty of brain cell interconnections, due to the excessive pruning of these axonal and dendritic connections, a process that appears to be at its height during adolescence (after puberty), although many now believe that the process begins before birth.

Steroids and schizophrenia: Steroid hormones influence a wide range of physiological functions from reproduction, stress, immune and inflammatory responses to behavior, motor function and even cognitive performance. It has been proposed that there is a relationship between disrupted forebrain development and signaling by the steroid-like hormone retinoic acid, which is produced by a developmental layer of cells derived from neural crest known as the mesenchyme (within the anterior neural tube), responsible for the induction and differentiation of adjacent epithelia. It is this induction mediated via interaction between the retinoic acid-producing mesenchyme and the anterior surface epithelium of the embryo that guides differentiation and PATHWAY FORMATION. It is thought that such a developmental flaw, either inherited or environmental, may constitute the "first hit" in the genesis of schizophrenia. Schizophrenia is extremely uncommon before adolescence and puberty, suggesting that the surge of altered steroid hormone biosynthesis associated with this stage of development, and possibly also those steroid hormones which are elevated in response to stress during these critical career-forming years of life, may also be implicated in the etiology of schizophrenia. Further, sex hormones have been shown to influence dopaminergic activity. Such surges in hormone levels may constitute the "second hit" in schizophrenia, facilitating excitotoxicity or oxygen radical formation that leads to neuronal damage. Indeed stress is well known as a common precursor of the first episode of psychosis. There is further evidence that altered levels of sex steroid hormones are associated with schizophrenia. Male schizophrenics were found to have higher levels of Luteinizing Hormone (LH) and testosterone than healthy subjects, presenting a puberty-like profile, and female schizophrenics higher levels of LH and lower levels of estrogen, in effect a menopause-like profile.

Schizophrenia: An inherited disordering of the mind?

Interest in an inherited causality for schizophrenia came from observations that schizophrenia often appeared to be clustered in families, an identical (monozygous) twin having a 40 to 50% chance of developing the illness, and a child of a schizophrenic parent around 10%. These rates are statistically high, but suggest neither classic Mendelian patterns of inheritance, nor exclude the effects of family or local environmental influences. A study of relatives of adoptees, in an attempt to minimize environmental influences, also found that schizophrenia is concentrated within biological families, the incidence of schizophrenia being slightly, but significantly elevated (5.1%) within the biological relatives of adopted schizophrenics. Psychiatric studies have suggested that schizophrenia is a disorder with multifactorial inheritance, i.e. involving many genes present in many

different locations throughout the bank of human 'chromosomal' information, as schizophrenia does not follow simple Mendelian inheritance. A disruption of genes that govern the neural crest-mediated, RA-dependent induction and differentiation in the forebrain such as Pax-6 & Gli-3 might be implicated in schizophrenia and perhaps crucially, the secreted extracellular matrix protein reelin (RELN) may play a role in schizophrenia. Linkage analysis of microsatellite regions in families with patterns of schizophrenia have revealed that genes predisposing susceptibility to schizophrenia may be present on chromosomes 1q, 5q, 6p, 8p, 13q, 15q, 18p and 22q, one of which (15q, locus 14), has been associated with the nicotinic receptor underlying the P50 deficit of schizophrenia. Regions on chromosomes 3, 9 and 20 have also been proposed to be candidates for schizophrenia genes. Thus not only may the many hundreds of genes involved in neuronal signaling and the development of the nervous system be potential factors in schizophrenia, but at least 8 chromosomal regions, each of which potentially may contain many genes which predispose to schizophrenia, have been variably associated with linkage analysis.

Other prevailing theories on the causation of schizophrenia: Five studies have suggested that being born or raised in an urban area is a risk factor for schizophrenia. An infectious agent transmitted through household crowding maybe responsible. Even neurotrophic viruses have been suggested. The Borna disease virus, an agent that was thought only to affect horse and sheep, causing brain inflammation through an immune response, is also a causative agent in schizophrenia. Other factors predisposing to schizophrenia include prenatal hypoxia, autoimmunity. Dohan's Hypothesis, proposes that Schizophrenia is an inherited predisposition which interacts with an overload of dietary proteins such as casein, glutens or gliadins. In a potentially related finding, exorphins, morphine-like compounds produced from milk protein which are taken up into the brain, are elevated in 95% of autistic and schizophrenic children, especially - casomorphin-7. In contrast Peet & Puri have proposed that schizophrenia is caused by a depletion of certain fatty acids in the membranes of nerve cells, symptoms which are ameliorated with dietary intake of EPA. Other neurotransmitter systems, not all of which have been identified to date, may be involved. For example norepinephrine (NE) is proposed to play a role in the induction of psychosis, and is further evidenced by the observation that a prenatal exposure of rats to amphetamines causes an increase in NE levels in the PFC. These observations are taken to be suggestive of a hyperactive NE system, resulting in psychotic behaviors. Other causative hypotheses take into account socio-developmental factors. Dysfunctional relations with, or absence of mother were thought by some to be schizophrenio-genic, although this argument is now widely refuted. Social stressors in urban settings are thought to facilitate the onset of disease in vulnerable persons. Indeed the loss of neuronal and/or connective tissues in schizophrenic patients due to the neurotoxic effects of over transmission of dopamine or excitatory amino acids may be attributable, in part if not in whole, to stress. There appears to be a connectivity between nodes (or clusters of neurons involved in processing) in the pre-frontal cortex, the thalamic nuclei and the cerebellum. Any disruption in this circuit may result in a cognitive impairment or dysmetria, leading to a difficulty in

prioritizing, processing, coordinating and responding to information: - central deficits in schizophrenia. Specific neuro-chemical disruption involving the release or reception of the neurotransmitters serotonin, glutamate, dopamine, acetylcholine, norepinephrine or GABA may be sufficient to wholly or partially mimic the symptoms of schizophrenia. Thus schizophrenia may be regarded as a heterogeneous dysfunction of cognitive and sensory processing.

THE ROLE OF FOUR 'S's (Stress, steroids, solitude and sensory deprivation)

Stress & Steroids: It is held that stress precipitates the positive psychotic symptoms of schizophrenia in many sufferers, and stress has been noted to precipitate positive symptoms in schizoid personality disorder sufferers who normally display only the negative symptoms of schizophrenia. Indeed stress is a common precursor of the first episode of psychosis following a long prodromal phase where only negative symptoms are seen. Stress induces the release of neuroactive steroids such as corticosterone from the hypothalamic-pituitary-adrenal axis, which like sex steroids including progesterone, have profound modulatory actions upon the function and expression of receptors and processes involved in the nervous transmission and processing of information. For example Cho and Little showed that perfusing slices from the ventral tegmental area, an area implicated in drug dependence and reward, with the steroid hormone corticosterone, released in response to stress, caused an increase in sensitivity of the activity of dopamine-releasing neurons to the three 'fast' glutamate receptor subtypes AMPA, kainate and NMDA. These pacemaker neurons release DA into the prefrontal cortex and nucleus accumbens as part of the neural mechanisms of reward and pleasure, and this increased sensitivity to glutamate is observed within 15 minutes of application of corticosterone, showing that stress can rapidly modulate neuronal activity and make neurons exquisitely sensitive to glutamate-mediated excitotoxicity. Indeed Gardner and others have proposed that mammals seek to maintain elevated DA levels within the Nucleus Accumbens, released from projections arising within the VTA, as a reinforcement of a positive activity, behavior or environment. Stress is catabolic, and pleasure, resulting in an elevation DA levels in the Nucleus Accumbens, PFC and hypothalamus is anabolic. So sex, food and social reward (for achievement or as a result of desirable or gainful behavior) can be argued to represent 'trophically' advantageous behaviors, and their reinforcement is mediated, at least in part, by enhanced activity within the dopaminergic system. However, this pleasure-seeking or reward behavior may be mimicked or bypassed by the use of psychoactive compounds which mimic or 'short-circuit' this enhancement of DA release, or else by abuses of food, video games or sexual activities, features of the densely-populated and technologically 'enriched' modern city environment. Excess calcium entry into the cell, which may occur due to cerebral ischemia (loss of oxygen), head injury, excitement, toxic drugs or even excessive nerve cell activity, causes damage to nerve cells and their connections (terminals), and at very high levels can even cause their death. Hence extreme stress as a result of traumatic life events or as a process of active social isolation, either alone or in combination with psychoactive drugs and possibly excessive excitatory transmission, may lead to the damage of intricate neuronal circuits and hence of cognitive processing and behavior. Excito-toxicity may in part explain the cognitive and

functional decline observed in schizophrenia, but may not be the only possible explanation for a decline in the degree of neuronal arborization (dendrites and axons) which have been suggested to occur in schizophrenia, and accordingly further experimental evidence must be afforded in support of this model.

Solitude & Sensory deprivation: Neurons extend processes during development and repair which are guided by factors to their programmed targets by molecules secreted from their target cells known as neurotrophins. However, the establishment of functional neuronal connections requires the secretion of signals from the outgrowing axon terminals. Indeed this process has been shown to occur even in the absence of synaptic signaling, as mice that lack the synaptic protein *munc 18-1*, essential for the release of neurotransmitters, nevertheless form 'normal' layered structures, fiber pathways and morphologically defined synapses during development. However, in the absence of functional synaptic transmission, the neurons in this 'knockout' mouse undergo programmed cell death (apoptosis), leading to widespread neuro-degeneration. Thus neurons require activity (neurotransmission) to survive, and if such activity is absent they will die as part of a pruning process that maintains only those neuronal connections which are useful, i.e. functional, perhaps only a fraction of the number that are originally formed. Thus there exists a dual influence of neuron upon target and of target upon neuron, by the release of neurotrophic factors such as Nerve Growth Factor (NGF). Thus there is both a genetically-programmed and use-dependent refinement of connections in the nervous system during development, and the more sophisticated cortical circuits associated with information processing, language and higher social functioning which emerge both later in evolution and during development, require functional validation for the establishment of their final patterns of connectivity. Brain cells in most people do not in fact die, when we age (excepting senile dementia, Alzheimer's etc.), rather the number of connections that they form diminish, and this connectivity is believed to correlate with a neuron's "computational power", and is enhanced in response to growth factors called neurotrophins which are released when neurons are stimulated, for example by new learning. Contextual learning in the hippocampus has been demonstrated to evoke the release of neurotrophin (BDNF), thereby increasing the extent of arborization of dendrites and thereby the potential computational power of the circuits involved. Conversely, removing neurotrophins causes dendrites to atrophy, which suggests that a lack of brain activity causes a loss of computational activity and mental decline. In fact neurotrophins help to maintain our intelligence and mental function via their release from active neurons, although it might be noted that neurons may be activated by a range of stimuli from sound through thought to smell and emotion. Thus sensory and social deprivation may cause a loss of computational power in regions of the brain involved in sensory processing, language and higher social intelligence, with the attendant consequences of social decline and lost opportunity. Such is the degree of plasticity present in the nervous system for the growth and regeneration of new cells and processes, that even after the loss of sight or even actual regions of the brain, function can be restored or replaced in whole or in part by other regions in a time and use-dependent manner. For example monkeys who lose part of their brains involved in the control of fine finger touch and

manipulation recover this function in neighboring areas over time with use in areas that previously had no such attributed function. Similarly, people who lose their sight after development show a shift in functional activation of their visual cortex from sight towards somato-sensory touch upon learning Braille. As stated before, it may be the case that the interpretations of an estimated 5% decrease in the volume of gray matter in the cortex observed in schizophrenia may be attributable to a decrease in the number of connections between cells, such as the dendrite and chandelier axon cartridge, rather than primarily a loss of neurons or glia per se. The poverty of thought, attention and memory associated with schizophrenia may reflect an acquired and progressive impoverishment of brain cell interconnections, due to degeneration, an excessive loss or pruning of axonal and dendritic connections.

The importance of environment to development and function : The prevailing research provocatively suggests that an enriched social environment is necessary for the development of 'normal' behavior and enhanced cortical thickening, as rats isolated after weaning develop behaviors reminiscent of schizophrenia and mice bred in enriched environments show both an increased cortical thickening and a greater number of hippocampal neurons. Indeed Romanian orphans raised in an isolated and impoverished environment showed a level of development that was so markedly retarded as to raise the question as to whether schizophrenia with its attendant loss of cognitive function is not a mild manifestation of an activity-dependent developmental disorder caused by social and sensory deprivation. Why should social contact be so important in cognitive performance, decision-making and the processing of sensory stimuli? The answer may be suggested in the formation of ocular dominance columns in the visual cortex which is itself dependent upon neural activity which is visually driven. By depriving one eye of visual information for several weeks during an early critical period of development (monocular deprivation) there was a marked change in the patterns of activation in the primary visual cortex. Cells in layer IV of the visual cortex were now activated only by input from the eye that had remained open, even if the other eye was still functional in the detection and transmission of light signals. In other words a constant sensory input from both eyes is required for the correct development of binocular processing of light information and the attendant orderly patterning of brain cells in the visual cortex. Anatomically, the terminal arbors of the axons of the lateral geniculate nucleus which were supplied by the uncovered eye were considerably more extensive than those supplied by the deprived eye. As an explanation for this phenomenon it has been found that there is an activity-dependent release of neurotrophic factors by cortical neurons and that this may affect the pattern and extent of wiring in the visual cortex. In fact this competitively-based loss of function from the covered eye could be specifically overcome by localized infusion with the neurotrophin NT-4. In plasticity there is hope. If sight is lost after its development the areas of the cortex attributed to vision show considerable plasticity in that they remodel from being activated primarily by visual information, to being activated by another sensory input, somato-sensory touch, and an acquired plasticity, (learnt) from the acquisition of Braille reading skills. Similarly social engagement and other high level forms of play and linguistic interaction, which constitute 'higher' primate behaviors and which are associated

with the evolutionary enlargement of the forebrain and association cortex, must not only be acquired through development, but must be used or else they may diminish. Neurons form connections in response to stimulation, at least in part induced by the activity-dependent release of neurotrophins, and if these 'activity-dependent' neuronal wiring patterns are not induced by sensory input they may not form (Romanian orphans), and if they are not maintained they may diminish or be 'functionally' lost (schizophrenia?). Another possibility is that stress or information 'overloading' (excessive activity) may cause damage to the neuronal processes of these cortical and sub cortical structures resulting in cognitive disruption and a loss of social functioning, concentration, disrupted speech etc.

CONCLUSION

Schizophrenia is a major debilitating, complex and costly illness that strikes 1% of the world's population. It is found in every society from the most primitive to the largest and most technologically advanced society. The risk of developing schizophrenia is almost equal in men and women, but gender differences do exist in the initial age of onset of the disease. Schizophrenia is characterized by three general types of symptoms: Positive symptoms (psychosis), Negative symptoms and Cognitive symptoms. Not all schizophrenic patients exhibit each of these symptoms, nor are these symptoms exclusive to schizophrenia. The excessive degree of cigarette smoking exhibited by schizophrenic patients suggests that they might be self-medicating to ameliorate to some extent the characteristic positive, negative and cognitive symptoms associated with the disease. These results have spurred the development of new pharmaceuticals specifically designed to modulate nicotinic receptor function. The initial results from clinical trials of these new drugs appear promising, potentially opening new avenues of treatment for this devastating disease. In the present review article, the authors have described the role of various neuromodulators such as Dopamine, Glutamate, Acetylcholine, Serotonin, GABA etc. responsible for causing schizophrenia in addition to FOUR 'S's (Stress, steroids, solitude and sensory deprivation). Treatment of psychotic disorders accounted for around 3.0 % of national health expenditures in developed countries. A greater understanding of the etiology of schizophrenia is, therefore, not only important from an individual standpoint, but also important for society as a whole.

Mice Vs Men for studying Schizophrenia

- Mice allow genetic manipulation and the rapid expression of traits.
- Mice can be bred in a well controlled environment.
- Mice do not sell stocks and shares, pass stressful examinations or manage their finances.
- The human mind does not allow an easy examination of the underlying molecular, genetic or biochemical reasons of mental illness.
- Men are heterogeneous and are brought up in a poorly controlled mixture of environment, experience and inheritance.
- Men allow linkage analysis and DNA testing of defined psychological profiles determined by psychometric parameters.

- The human mind allows the study of the dynamic functioning of the brain in response to fixed stimuli, measured by imaging or electrically evoked potentials.
- Men sell stocks and shares, pass stressful examinations, face interviews or manage their finances, but they do behave socially and trophically.

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