Are There Neurochemical Indicators of Risk for Schizophrenia?

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Abstract

The genetic predisposition for certain forms of schizophrenia may involve heritable abnormalities in the functioning of neurochemical systems that project to and modulate limbic brain structures. However, with regard to both dopaminergic and serotonergic systems, there is little evidence that either basal cerebrospinal markers or plasma markers predict increased risk for the development of schizophrenia. Either their validity as correlates of brain monoamine function is uncertain or they are highly dependent upon clinical state. Both (1) platelet and neuroendocrine markers of serotonergic function and (2) an individual's capacity to decrease plasma homovanillic acid concentrations following neuroleptic blockade appear to be less state dependent, and these are worthy of further study as markers of risk for the development of schizophrenia.


The response of schizophrenia patients to neuroleptic drugs provided one of the first types of strong evidence that schizophrenia was a neurobiological rather than psychological illness (Carlsson 1978). For many years, the neurobiological basis of schizophrenia was thought to be mainly neurochemical in nature (see Meltzer and Stahl 1976, and Carlsson 1978 for reviews). It was not until the introduction of computerized tomographic studies of brain structure in schizophrenia patients that pathogenetic theories of schizophrenia had to consider the possibility that the illness might have structural as well as neurochemical elements (Roberts 1990). Many recent theories of the etiology or pathogenesis of schizophrenia propose an integrated mechanism that includes structural as well as functional neurochemical components.

With the discovery that there were structural brain alterations in schizophrenia, it became attractive to hypothesize that some aberration in the developmental mechanisms that determine brain structure might underlie the heritability of schizophrenia (Bruton et al. 1990). For example, one could propose that a heritable defect in the attachment molecules that allow developing neurons to ride glial filaments to their eventual anatomical destinations could be the basis of the pathogenesis of schizophrenia (Jones and Murray 1991). Several studies were undertaken to determine whether structural brain abnormalities characteristic of schizophrenia were more common or severe in patients with strongly positive family histories (e.g., Farmer et al. 1987). Studies of monozygotic twins (genetically identical) discordant for schizophrenia addressed this point more powerfully by showing that structural brain abnormalities characteristic of schizophrenia were present in almost all affected twins and in no unaffected twins (Reveley et al. 1982; Suddath et al. 1990). While these studies do not rule out the possibility that particular forms of schizophrenia might be caused by...
heritable abnormalities of brain structure, they do suggest that such forms of the disorder are not common or that heritable abnormalities of brain development need to be magnified by environmental factors before they can be observed with contemporary brain imaging techniques.

These findings also restore interest in the possibility that certain forms of schizophrenia may be caused by heritable abnormalities of neurochemical systems within brain structures anatomically altered during development. Gross anatomical as well as cytoarchitectural abnormalities suggestive of developmental pathology have characteristically been found within the structures of the limbic system, such as the hippocampus, perirhinal cortex, and cingulate cortex (Roberts 1990). These structures have rich monoaminergic inputs (see below). Therefore, one could hypothesize that heritable abnormalities of monoaminergic systems might play a role in schizophrenia by failing to correct for the dysfunction of intrinsic neurotransmitter systems (e.g., glutamate) that have been damaged by developmental anatomical irregularities. However, to be detectable as markers of risk for schizophrenia, these adaptational failures would have to be somewhat generalized and would have to be measurable during at least some clinical states of the illness.

Ascending midbrain projections of three major monoamine neurotransmitter systems—dopamine (DA), serotonin (5-HT), and noradrenaline (NE)—modulate the function of intrinsic excitatory amino acid neurotransmitter systems within limbic structures. Abnormalities in the interaction of these monoamines, particularly DA, with glutamate have been emphasized in recent hypotheses of the pathogenesis of schizophrenia (Carlsson 1988; Reynolds 1989; Carlsson and Carlsson 1990; Lucchins 1990; Csernansky et al. 1991). In this article, we will review the utility of measures related to the functioning of brain DA and 5-HT systems as markers of risk for schizophrenia. Since one of the major outflows of the limbic system is the hypothalamus, selected neuroendocrine measures linked to central nervous system DA and 5-HT function will also be reviewed. Markers related to the functioning of NE and the excitatory amino acids will not be reviewed here because research in these areas is less well developed; a review of preliminary data is available elsewhere (Meltzer 1987).

Markers of Risk Related to DA Function

Clinical indices of DA function in the plasma and cerebrospinal fluid (CSF) of schizophrenia patients have been analyzed repeatedly (for a recent review, see Davis et al. 1991). In CSF, DA (in free and sulfated forms) and the end products of its metabolism—homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC)—are available for measurement (Scheinin 1985). Plasma levels of DA and DOPAC have been found to be too low for reliable measurement; thus, plasma HVA has been studied most widely as an accessible peripheral marker of brain DA function (Guelfi and Csernansky 1989). In addition to neurochemical markers of DA release and turnover, proteins involved in the uptake and metabolism of DA have been the object of study. Among these proteins, monoamine oxidase (MAO) has been the object of exhaustive studies in schizophrenia patients and in individuals at high risk for schizophrenia. However, platelets have been the nearly exclusive source of the enzyme for these studies, and it is important to remember that the MAO-B found in platelets is most likely present to metabolize 5-HT rather than DA (Stahl et al. 1982).

Others have reviewed the utility of lower levels of platelet MAO-B activity as a genetic marker of risk for schizophrenia (Siever and Coursey 1985; Delisi et al. 1987) and have come to generally negative conclusions. Although there is an association between lower platelet MAO-B activity levels and schizophrenia (Wyatt et al. 1979), it can probably be accounted for by gender and race factors (Meltzer and Zuterek 1987) or by incidental environmental factors (e.g., neuroleptic treatment, poor diet, alcohol exposure) commonly found in schizophrenia patients (Friedhoff and Miller 1980; Sullivan et al. 1980; Kemali et al. 1985). In addition, although there is reasonable evidence that platelet MAO-B activity levels are under genetic control (Oxenstierna et al. 1986), the allele responsible for lower activity levels appears to be more common in the general population than would be consistent with a causative role for a relatively uncommon disorder such as schizophrenia (Rice et al. 1984). For these reasons, platelet MAO-B activity has generally been rejected as a marker of risk for schizophrenia and will not be discussed further in this review.

Heritable alterations of the function or expression of postsynaptic DA receptors are also plausible neurochemical markers of risk for schizophrenia. On lymphocytes,
[\textsuperscript{3}H]spiperone binding sites have been assessed (LeFur et al. 1980; see also Wodarz et al. 1992 for a review). Although [\textsuperscript{3}H]spiperone is usually the ligand of choice for studies of brain DA D\textsubscript{2} receptors, whether these lymphocyte binding sites represent true DA D\textsubscript{2} receptors remains unknown. While the functional status of such protein markers is unlikely to exactly reflect their counterparts in the brain, it is plausible that heritable alterations affecting their function would be represented in both brain and platelets (Stahl et al. 1982).

Measures of prolactin (PRL) and somatotropin, or growth hormone (GH), have been used for both static and dynamic assessments of DA function in the central nervous system. However, their use as markers of risk for schizophrenia is limited by evidence that they are state dependent. The measurement of PRL concentrations in plasma has received the most extensive study. The plasma GH response to a variety of DA agonist challenges has also been investigated extensively.

**Reliability, Validity, and Other Measurement Issues.** The ability to measure small polar molecules, such as DA and its metabolites, DOPAC and HVA, has improved greatly in recent years. High-pressure liquid chromatography (HPLC), using reverse phase separation and electrochemical detection techniques (Caliguri and Mefford 1984), has generally replaced other methods of measurement, including HPLC with fluorometric detection, gas chromatography with mass spectroscopy, and enzymatic assays. DA and its metabolites, derived from either plasma or CSF, can be assayed with excellent reliability. However, the validity of these measures as indices of the level of function of the DA system is far less certain (Scheinin 1985). With respect to DA and the other monoamines, one generally assumes that the concentrations of their metabolites in plasma or CSF are proportional to the amount of transmitter released, recaptured by the presynaptic terminal, and metabolized (Scheinin 1985). However, the validity of this assumption remains unproven and is difficult to test.

The interpretability of HVA in CSF is also confounded by the fact that there is a marked gradient in the concentration of this metabolite from the higher levels found in the lateral ventricles to the lower levels found in the lumbar space from which samples are taken. This gradient is attributable to the fact that nearly all of the HVA found in CSF is derived from brain rather than spinal cord metabolism and that HVA is systematically transported from CSF into the blood all along the spinal column (Scheinin 1985). Nonetheless, neuroleptic drugs that acutely increase brain DA release and turnover in animal studies also increase CSF and plasma HVA concentrations in humans. Perhaps more important, animal studies have shown that just as tolerance develops to the HVA-elevating effects of neuroleptics in subcortical brain structures, CSF and plasma HVA concentrations also return toward baseline levels over several weeks of neuroleptic treatment (for a review, see Davis et al. 1991). Therefore, with respect to the acute effects of neuroleptics on brain DA systems and the capacity of brain DA systems to undergo adaptive changes in response to receptor blockade over time, CSF and plasma HVA concentrations appear to be reasonably valid and obtainable indices of brain DA function in humans.

The reliability and validity of [\textsuperscript{3}H]spiperone binding sites on animal and human platelets as a marker of DA D\textsubscript{2} receptor expression or function is highly questionable. While the binding of [\textsuperscript{3}H]spiperone to these sites is saturable and of high affinity, evidence for stereo-specificity is weak and the rank order of affinity for DA D\textsubscript{2} receptor antagonists does not precisely match the profile of brain DA D\textsubscript{2} receptors (Wodarz et al. 1992). Furthermore, only intact lymphocytes bind [\textsuperscript{3}H]spiperone; no binding sites are found in prepared membranes. The latter problem may explain, at least in part, why the binding site density and affinity values reported by various laboratories differ so much. The binding of [\textsuperscript{3}H]spiperone to intact lymphocytes may represent a non-specific ligand entrapment phenomenon rather than a neurotransmitter receptor (Maloteaux et al. 1983). In addition, Wodarz et al. (1992) have shown that lymphocyte [\textsuperscript{3}H]spiperone binding can be blocked by GBR-12929, a specific ligand for the DA transporter protein.

Reliable and sensitive radioimmunoassays for PRL (Hwang et al. 1971) and GH (Schalch and Parker 1964) are available. However, the measurement of PRL following an apomorphine challenge has been shown to have poor within-subject reliability (Pandey et al. 1977). DA is released into the hypothalamic-hypophyseal portal system, where it has access to the anterior pituitary and interacts with D\textsubscript{2} receptors on lactotrophs to tonically inhibit PRL release (Moore and Demarest 1982). In this way,
serum PRL levels can inversely reflect the activity of hypothalamic dopaminergic neurons or the sensitivity of pituitary D2 receptors. Stimulation of GH secretion is mediated by DA through both hypothalamic GH-releasing hormone and suppression of somatostatin release (Wass 1983). However, NE and 5-HT neurons also promote GH release in humans (Lal and de la Vega 1975), and the interaction among these systems for GH regulation remains unclear. Dysregulation of GH secretion in schizophrenia appears to reflect a disturbance above the level of the pituitary, possibly in hypothalamic postsynaptic DA receptors (Mayerhoff et al. 1990).

The relationship between tuberoinfundibular DA activity and mesolimbic or nigrostriatal DA activity remains unclear and is still under investigation in a variety of animal and human models. In humans, the ability of acute treatment with neuroleptics to block pituitary D2 receptors and produce hyperprolactinemia is directly correlated with the medication's antipsychotic potency (Langer et al. 1977). However, known differences between tuberoinfundibular and other DA neurons further compromise the validity of equating their function. These differences include the absence in the tuberoinfundibular pathway of an effective high-affinity uptake system and autoreceptors for DA, along with the ability to increase turnover of DA in response to PRL (Moore and Demarest 1982). Despite these problems, specific clinical conditions in patients with schizophrenia have produced indirect evidence for a relationship between both mesolimbic and nigrostriatal DA activity and tuberoinfundibular activity.

Normal Ranges and Familiality. In general, there is wide interindividual variation in the concentrations of plasma and CSF monoamines and monoamine metabolites. This variation is largely attributable to the many state-dependent and potential genetic factors that influence these concentrations (Scheinin 1985). In normal subjects, CSF concentrations of both HVA and 5-hydroxyindoleacetic acid (5-HIAA) tend to increase with age (Gottfries et al. 1971). Furthermore, the tendency for variability is greater among groups of patients with psychiatric disorders, particularly schizophrenia (Meltzer and Stahl 1976). Some techniques have been suggested for decreasing the effect of nuisance variables on these neurochemical measures, such as controlling physical activity, smoking, or diet; selecting a particular CSF aliquot; or holding the subject in a particular position before performing the lumbar puncture (Gateless et al. 1984; Davidson et al. 1987). However, the effectiveness of such measures in reducing all unwanted sources of interindividual variability is uncertain. Some investigators have attempted to reduce peripheral contributions to plasma HVA by administering debrisoquin, a peripheral inhibitor of DA's metabolism by MAO to HVA (Maas et al. 1985). However, this technique also has significant shortcomings. Debrisoquin causes moderate to severe nausea and hypotension in many subjects, and there may be individual genetic variability in debrisoquin metabolism (Steiner et al. 1985). Finally, Kopin et al. (1988) have suggested that the contribution of HVA from peripheral NE metabolism can be dealt with by correcting plasma HVA values for the amount of plasma methoxyhydroxyphenylglycol (MHPG) concurrently measured.

There have been very few studies of the heritability of plasma and CSF neurochemical measures of monoamine turnover. One group studied CSF concentration values for HVA, MHPG, and 5-HIAA in small groups of monozygotic twins, dizygotic twins, siblings, and unrelated males (n = approximately 15 per group; Oxenstierna et al. 1986). Path analysis indicated that although familial factors influence all of these concentrations, none of them were under any major genetic influence. However, the sample sizes were admittedly small, and the technique of path analysis may be insensitive for detecting the influence of single major genes. Oxenstierna et al. (1986) also examined the heritability of platelet MAO and dopamine-β-hydroxylase in these same samples and found strong evidence of genetic influence for these markers.

The normal ranges for plasma PRL and GH concentrations are well known. However, antipsychotic treatment can confound the assessment of baseline as well as apomorphine-induced changes in these concentrations (Scheinin et al. 1985). Assessments of PRL and GH following acute DA agonist or neuroleptic challenges have been made in schizophrenia patients. However, to our knowledge, no work has been conducted on the familiality of PRL and GH concentrations, in part owing to potential difficulties in performing DA agonist and antagonist challenge paradigms in normal subjects.

Involvement in the Pathophysiology of Schizophrenia and State Independence. The DA hypothe-
sis of schizophrenia has been emphasized for almost three decades (Meltzer and Stahl 1976; Davis et al. 1991), and a variety of studies have been performed to determine whether plasma and CSF HVA concentrations can distinguish schizophrenia patients from control subjects and from patients with other psychiatric disorders. However, studies of such monoamine markers have had conflicting results (Wyatt 1986), perhaps because state-versus-trait issues have been difficult to resolve. CSF HVA concentrations in schizophrenia patients and controls generally do not differ. However, occasional group differences have been found in conjunction with groupings of particular symptoms. For example, Lindstrom (1985) found that schizophrenia patients had lower CSF HVA concentrations than control subjects, and the levels of these metabolites were directly correlated with the amount of social interest displayed and inversely correlated with lassitude and slow movements. Others have also found that decreased CSF HVA levels are correlated with a poor prognosis (Bowers 1974). Further, higher than usual plasma HVA levels have been correlated with severity of psychotic symptoms during acute relapse (Davis et al. 1985), and plasma HVA levels fall as psychosis remits in response to neuroleptic treatment (Pickar et al. 1986). These and other observations have led some experts to suggest that it is the capacity of presynaptic DA function to undergo adaptive decreases in response to neuroleptic-induced postsynaptic DA receptor blockade that determines the relative success of neuroleptic treatment (Friedhoff 1988).

These studies also suggest that plasma and CSF HVA concentrations are poor candidates as markers of risk in schizophrenia because they are so highly state dependent. However, the utility of markers based on the capacity of an individual’s presynaptic DA functions to adapt to the presence of neuroleptic-induced receptor blockade has not yet been tested. Bower and coworkers have shown in several studies that schizophrenia patients can be divided on the basis of whether plasma HVA concentrations fall during neuroleptic treatment and that neuroleptic response is superior in patients who show adaptive decreases over time (Bowers and Heninger 1981; Bowers et al. 1984, 1987). Further, neuroleptic responsivity is, in general, a stable trait in schizophrenia patients (Kolakowska et al. 1985), although in at least one small study of siblings concordant for schizophrenia the agreement for neuroleptic responsivity between siblings was no greater than chance (DeLisi and Dauphinais 1989). The heritability of this trait should be tested in schizophrenia patients and in normal subjects. However, although there are no serious obstacles to carrying out such experiments with schizophrenia patients, neuroleptics are not easily given to normal subjects because of unpleasant extrapyramidal side effects and the risk of developing less reversible movement disorders (e.g., tardive dyskinesia).

In addition to these markers of presynaptic DA function, measures of postsynaptic DA receptor function or density might also be plausible markers of risk in schizophrenia. Correlations between antipsychotic potency and DA D2 receptor affinity across neuroleptics led schizophrenia researchers to suggest that there might be DA D2 receptor abnormalities in the schizophrenic brain (see Csernansky et al. 1991 for a review). Postmortem measurements of DA D2 receptors in the caudate nucleus, putamen, and nucleus accumbens have shown increased densities in the brains of schizophrenia patients. Although some investigators have suggested that this difference may be due to chronic neuroleptic treatment (Mackay et al. 1982), DA D2 receptor density values in large schizophrenia populations have a bimodal distribution not easily attributable to differences in neuroleptic exposure (Seeman et al. 1987).

From a practical point of view, brain DA receptor density values derived from postmortem studies have no utility as markers of risk for schizophrenia. However, positron emission tomography (PET) studies of basal ganglia DA D2 receptor density in living schizophrenia patients, particularly those who have never been treated with neuroleptics, have been possible for several years. Unfortunately, the two major groups of investigators employing this technique disagree as to whether PET measures of DA D2 receptor density distinguish schizophrenia patients from control subjects. Wong et al. (1986) found approximately twofold elevations in DA D2 receptor densities in a small group of drug-naive American patients, whereas Farde et al. (1990) found no difference in similarly small groups of Swedish drug-naive patients and controls. The difference in the outcome of these studies might be accounted for by differences in the patient samples. However, Seeman et al. (1990) recently reported that the use of raclopride for PET studies under-
estimates DA D_2 receptor densities and could obscure group differences. Other obvious barriers to the use of PET assessments of brain DA systems as indicators of risk are cost and the necessity of exposing each subject to nontrivial doses of radiation.

Blood PRL concentrations do not distinguish schizophrenia patients from normal control subjects (Meltzer et al. 1974) and patients with other psychiatric illnesses (Whalley et al. 1989). Similarly, there are no significant differences in CSF PRL levels between schizophrenic patients and control subjects (Wode-Helgodt et al. 1977; Rimón et al. 1981). Comparisons of unmedicated schizophrenia patients and control subjects have revealed no differences in either the degree of PRL suppression by apomorphine (Meltzer et al. 1984) or the increase in PRL induced by metoclopramide (Crow et al. 1986). However, PRL concentrations during neuroleptic treatment have been found to be related to acute neuroleptic response (see Meltzer et al. 1983 for a review), early relapse (Brown and Laughren 1981), positive psychotic symptoms (Csernansky et al. 1986; Newcomer et al. 1992), and tardive dyskinesia (Tamminga et al. 1977; Csernansky et al. 1986; Newcomer et al. 1992). Correction of PRL values for plasma neuroleptic concentrations (Swigar et al. 1984) and the use of patients with normal cerebral ventricular size (Kleinman et al. 1982) may improve the strength of such relationships. These results suggest that plasma PRL may serve only as a peripheral marker for DA activity in nigrostriatal and mesolimbic pathways during specific clinical states.

The effect of neuroleptic treatment on apomorphine- or L-dopa-induced changes in GH has been investigated as a measure of hypothalamic-pituitary DA dysregulation (Lal 1988). Cleghorn et al. (1983b) reported that drug-free schizophrenia subjects with active positive symptoms have higher GH responses to apomorphine than do normal subjects. However, high interindividual variance in GH response has been observed. GH response is blunted in schizophrenic patients, consistent with the seemingly paradoxical hypothesis of DA receptor hyposensitivity (Meltzer 1984). However, a blunted GH response does not reliably distinguish schizophrenia subjects from patients with other psychiatric disorders (Sharma et al. 1990). Variability of results across studies is common and could be explained by differences among the study subjects.

Other state-dependent contributors to the variance in GH responses have been identified. For example, an inverse relationship has been observed between peak GH responses and the duration of illness and neuroleptic exposure (Rotrosen et al. 1979; Meltzer et al. 1984). Unfortunately, most studies have used subjects with extensive treatment histories (not necessarily limited to neuroleptics) and highly variable prestudy treatment withdrawal periods (Meltzer 1984). Age, weight, sex (Meltzer et al. 1984; Sharma et al. 1990), ventricular enlargement (Jeste 1981), relapse (Cleghorn et al. 1983a), and the severity of positive symptoms (Cleghorn et al. 1983b; Meltzer et al. 1984) may also influence the GH response. Finally, the relationship between negative symptoms and GH responsivity remains unclear (Tamminga et al. 1977; Meltzer et al. 1984), possibly reflecting population differences in confounding variables across studies.

Association With Increased Risk for Schizophrenia. Among groups at increased risk for schizophrenia are the first-degree relatives of schizophrenia patients, particularly children who have not attained the usual age of onset for schizophrenia. However, understandably, studies of CSF or plasma DA turnover markers have not been done in these populations. There is a natural reluctance to perform invasive tests in children; in addition, some markers of interest (i.e., changes in plasma HVA concentrations following neuroleptics or stimulants) would involve placing these individuals at risk for serious neurologic side effects or precipitation of a first psychotic episode.

Among the relatives of schizophrenia patients, an increased prevalence of schizophrenia-spectrum disorders, (e.g., schizotypal personality) has been found (Torgeron 1985). The risk for schizophrenia-spectrum disorders is also elevated among the relatives of patients with schizotypal personality (Siever et al. 1990). These findings suggest that neurochemical studies of patients with schizophrenia-spectrum disorders, whether or not they are known to be related to a schizophrenia patient, are also relevant to this discussion.

Siever and colleagues have reported that both plasma (Siever et al. 1991) and CSF HVA (Siever 1991) are elevated in individuals with schizotypal personality compared with nonpsychiatric controls. This agreement in the direction of changes between plasma and CSF HVA is somewhat unusual, given that CSF HVA tends to be de-
increased in schizophrenia patients while plasma HVA tends to be increased (Davis et al. 1991). Nonetheless, these findings suggest that increases in brain dopaminergic function may be present in some groups of high-risk individuals. Given that patients with schizotypal personality disorder do undergo neuroleptic treatment from time to time, studies of neuroleptic-induced changes in plasma and CSF HVA levels should be possible in the future.

With regard to markers of postsynaptic DA function, [H]-spiperone binding sites on lymphocytes have been studied in the relatives of schizophrenia patients. Although the reservations concerning this marker (discussed above) should not be forgotten, increased densities of these binding sites were found in approximately one-third of the well relatives of schizophrenia probands in one study (Bondy and Ackenheil 1987). This finding has not yet been replicated by an independent group.

Sautter et al. (1987) have investigated the familiality of the GH response to apomorphine in patients with schizophrenia. Probands were categorized into high, intermediate, and low response groups on the basis of the GH response to apomorphine. Sautter et al. found that GH response differentiated the relative risk of finding schizophrenia-spectrum disorders in the first-degree relatives of probands: probands with high GH response had the lowest familial risk. This report suggests that specific schizophrenia subtypes, distinguishable by means of a GH marker, may carry distinct familial risk for transmission of the affected state.

Cost-Effectiveness. The cost and level of difficulty of obtaining these markers of DA function vary considerably. Assays for HVA are inexpensive, and plasma is easily obtained. For binding site assays on peripheral blood cells, the costs are relatively modest but intact live cells are needed, and even if these binding sites could be detected on frozen membranes in the future, the stability of prepared membranes for long periods of time is questionable. CSF is not easily obtained, which basically precludes making these measurements on anyone other than hospitalized patients and those who may be more used to invasive procedures. Finally, assessments of brain neuroreceptors with PET scanning is practically precluded in large-scale studies because of cost. However, if suitable ligands and techniques for image resolution are developed for single photon emission computed tomography in the future, this technology may offer a substitute.

All of the plasma endocrine markers discussed are easily obtained by blood sampling, and the cost of the various assays is modest. The use of neuroleptic or DA agonist challenge protocols requires time and repeated blood samplings following an appropriate challenge. While the actual cost of obtaining these measurements in patients is modest, the risks associated with the potential complications of performing neuroleptic or DA agonist challenges in well subjects may be prohibitive.

Markers of Risk Related to 5-HT Function

Studies of 5-HT have also contributed in several ways to our understanding of the pathogenesis of schizophrenia. Decreases in central indices of 5-HT function (e.g., CSF 5-HIAA) have been linked to positive symptoms and impulsivity, whereas increases have been linked to negative symptoms. In addition, preliminary data indicate that increased CSF 5-HIAA levels are associated with a genetic risk for schizophrenia. In addition, changes in PRL, GH, and adrenocorticotropic hormone (ACTH) blood levels following 5-HT receptor agonists and antagonists, as well as 5-HT precursors, reuptake inhibitors, and releasing agents (e.g., fenfluramine) have been investigated as markers of functional brain 5-HT activity in psychiatric patients.

Reliability, Validity, and Other Measurement Issues. Plasma concentrations of 5-HT or 5-HIAA have not been widely studied in schizophrenia because diet can greatly confound the utility of these markers as indices of brain 5-HT function. The gradient for CSF 5-HIAA concentrations within the CSF column is smaller than that for CSF HVA; the difference is attributable to the fact that while brain-derived 5-HIAA is transported out of the CSF all along the spinal canal, 5-HIAA derived from spinal cord 5-HT metabolism is simultaneously being added to replace it (Scheinin 1985). Typical neuroleptics, such as haloperidol, are not known to alter CSF 5-HIAA concentrations (Scheinin 1985); however, tricyclic antidepressants decrease both CSF 5-HIAA and MHPG concentrations (Potter et al. 1985).

Platelet 5-HT uptake sites, MAO-B, and 5-HT2 receptors play critical roles. 5-HT is taken up from the plasma, stored, and then released to bind to 5-HT2 receptors on other platelets, triggering a characteristic shape change and ag-
ggregation (Stahl et al. 1982). Biochemical parameters of these markers are analogous to central nervous system markers, and their measurement is reliable and interpretable so long as there are no confounding medical conditions that affect platelet production or functioning (e.g., alcohol-induced splenomegaly).

The oral use of the 5-HT precursors L-tryptophan (LTP) and 5-hydroxytryptophan (5-HTP) for serotonergic neuroendocrine challenges produces unsatisfactory variability in PRL and GH responses (Kato et al. 1974; Woolf and Lee 1977). However, intravenous infusion of 5-HTP or LTP produces more reliable rises in PRL and ACTH or cortisol levels (Nash and Meltzer 1991). Studies in which specific 5-HT antagonists were used to block LTP- or 5-HTP-induced changes in hormone levels suggest a role for both 5-HT₁ and 5-HT₂ receptor mechanisms (Nash and Meltzer 1991). The use of 5-HT reuptake inhibitors for neuroendocrine challenges has so far been disappointing; little evidence for a significant or reliable effect on pituitary activity has been found (Meltzer and Nash 1988). However, the 5-HT releasing agent, fenfluramine, has been reported to reliably increase plasma PRL concentrations (Quatrone et al. 1983) but not ACTH or cortisol concentrations (Mühlbauer and Müller-Oerlinghausen 1985). Direct 5-HT agonists such as buspirone (Meltzer et al. 1983) and ipsapirone (Lesch et al. 1989) may offer new probes of 5-HT function, since they possess partial 5-HT receptor selectivity. Finally, Meltzer et al. (1987) reported that the potent 5-HT₂ receptor antagonist, clozapine, significantly inhibited MK-212-induced cortisol secretion.

**Normal Ranges and Familiality.** CSF 5-HIAA concentrations vary widely across individuals and do not appear to be determined in large part by genetic factors (see above). Normal ranges for pituitary hormone responses are available for the majority of the neuroendocrine challenge paradigms. However, no studies have been done to determine the heritability of such measures.

**Involvement in the Pathophysiology of Schizophrenia and State Independence.** CSF 5-HIAA concentrations have been studied widely as a neurochemical marker for schizophrenia. While CSF 5-HIAA concentrations do not distinguish schizophrenia patients from comparison groups (Post et al. 1975), significant relationships to symptom groupings have been found in some groups of schizophrenia patients. Ashcroft et al. (1966) found that CSF 5-HIAA concentrations were lower in "acute" than in "chronic" schizophrenia patients, and this finding has been replicated (Bowers 1978). Also, lower concentrations of CSF 5-HIAA have been associated with increased risk for violent suicide in schizophrenia patients (Ninan et al. 1984). Furthermore, both Post et al. (1975) and Lindstrom (1985) have demonstrated inverse correlations between CSF 5-HIAA concentrations and the severity of psychotic symptoms.

Others have suggested that higher CSF 5-HIAA concentrations are related to greater severity of negative schizophrenic symptoms. Bowers (1978) reported a significant direct correlation between emotional withdrawal and higher concentrations of CSF 5-HIAA concentrations following probenecid administration. King et al. (1985) showed that two measures of 5-HT function, CSF 5-HIAA concentrations and platelet 5-HT concentrations, correlated directly with the severity of autistic mannerisms and posturing in schizophrenic patients (King et al. 1985). Finally, Csernansky et al. (1990) showed that CSF 5-HIAA concentrations correlate directly with negative symptoms, poor work history, and inattention as assessed by Wechsler Adult Intelligence Scale-Revised (Wechsler 1981) subscale scores.

Few investigators have addressed potential differences between schizophrenia patients and normal subjects in the pituitary hormone response to serotonergic challenges. Lerer et al. (1988) reported that neuroleptic-free schizophrenia patients have a blunted PRL response to fenfluramine in comparison with age- and sex-matched normal controls. The utility of specific 5-HT agonists and antagonists for assessing differences between schizophrenia subjects and various control populations remains promising but is largely untested. Iqbal et al. (1991) recently reported that schizophrenic subjects showed a significantly lower cortisol and PRL response following infusion of the nonselective 5-HT receptor agonist 1-(m-chlorophenyl) piperazine than did normal subjects.

**Association With Increased Risk for Schizophrenia.** Negative symptoms may be overrepresented among the family members of schizophrenia patients (Moldin et al. 1990), and this finding suggests that 5-HIAA concentrations might be similarly increased in such individuals. In preliminary support of this hypothesis, Sedvall and Wode-Helgodt (1980) and Lindstrom...
(1985) reported higher CSF 5-HIAA concentrations in schizophrenic patients with a strong positive family history of the disorder. Sedvall et al. (1980) also reported higher CSF 5-HIAA concentrations in normal subjects with a positive family history of schizophrenia. Studies of neuroendocrine measures of 5-HT function and platelet markers of 5-HT function have not yet been undertaken in individuals at increased risk for schizophrenia.

Cost-Effectiveness. Among the various markers of 5-HT function, those obtained by collecting platelets are the least intrusive and most economical. Although CSF 5-HIAA concentrations have been most thoroughly studied to date, it is impractical to obtain CSF in many populations. Neuroendocrine measures may require repeated plasma sampling following an oral or intravenous challenge, but costs are generally modest. The compounds used for obtaining the dynamic neuroendocrine tests of 5-HT activity do not, in general, carry the same risks for normal subjects found in the analogous tests of DA-related neuroendocrine activity.

Recommendations for Future Research

The literature strongly suggests that no simple marker of brain DA activity serves adequately as a marker of risk for developing schizophrenia. More studies could be performed to determine whether individuals at high risk for schizophrenia have altered plasma or CSF HVA values. However, these readily accessible markers of DA function in blood and CSF appear to be largely state dependent. Markers of DA receptors on lymphocytes are difficult to validate and those derived from PET studies of the human brain are too costly to perform.

It is intriguing to consider that an individual's capacity to decrease presynaptic DA release and turnover following neuroleptic blockade might be a more suitable trait variable. This capacity has not been studied in siblings concordant for schizophrenia, but such studies are feasible and might give evidence of heritability. Of course, to enable the study of this type of marker in normal subjects or the well relatives of schizophrenia patients, an alternative to treating the well subject with neuroleptics for several weeks would be required.

Increased efforts should also be made to determine the utility of measures of 5-HT function as markers of risk for schizophrenia. Markers worthy of further study include platelet 5-HT₂ receptor and 5-HT uptake site density and affinity. In addition, the signal transduction system related to 5-HT₂ receptors could be studied in fresh platelets. As an alternative to using platelets as a peripheral 5-HT model system, neuroendocrine challenge studies using the most selective receptor agonists and antagonists also deserve increased attention.

References


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Nominations are being sought for the 1994 American Psychological Foundation/Gralnick Foundation Award for schizophrenia research.

Candidates for this award of $1,500 must demonstrate an exceptional contribution to schizophrenia research with emphasis on the discovery and/or treatment of the earliest signs of schizophrenia, emphasizing the psychosocial aspects as opposed to the biological aspects of the disease process. Preference will be given to persons working in a psychiatric facility.

Individuals must submit applications to the American Psychological Foundation by March 1, 1994. To request an application or additional information, please contact:

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