Pineal Melatonin in Schizophrenia: A Review and Hypothesis

by Reuven Sandyk and Stanley R. Kay

Abstract

It has long been suggested that abnormal functions of the pineal gland may be implicated in the pathophysiology of schizophrenia. We present evidence proposing that diminished melatonin secretion may be associated with the pathophysiology of a subgroup of schizophrenic patients characterized by cerebral atrophy and ventricular enlargement, negative symptoms, impaired cognitive and psychosexual development, onset at pubescence, poor response to neuroleptic medication, and possible increased risk of extrapyramidal symptoms. This view holds that a subnormal plasma melatonin level may be a marker of a subgroup of schizophrenia and may also denote a specific genetic susceptibility.

It is now widely assumed that schizophrenia is not a single disease entity but a biologically heterogeneous collection of possibly distinct subtypes (Wyatt et al. 1981). One possible biologically and clinically meaningful subgroup of schizophrenic patients are those defined as having subtle morphological brain abnormalities associated with enlarged cerebral ventricles according to computed tomography (CT) scan criteria (Weinberger et al. 1979, 1980; Rossi et al. 1988). Schizophrenic patients with enlarged lateral ventricles (at least two standard deviations above mean control values) have in some studies demonstrated poorer performance on neuropsychological testing, more disordered smooth pursuit eye tracking, poorer premorbid adjustment, more negative symptoms, higher incidence of suicide attempts, and greater susceptibility to develop abnormal involuntary movements as compared with schizophrenic patients who have normal ventricular size (Weinberger et al. 1980; Andreasen et al. 1982; Potkin et al. 1983; Owens et al. 1985). It is noteworthy, however, that the association of ventricular enlargement with measures of negative symptoms or neuropsychological impairment in schizophrenia was not observed in all studies (Pfefferbaum et al. 1988).

Biochemically, there is evidence that excess dopaminergic activity is less prominent in this subtype of schizophrenia, which is characterized by a generally poorer response to neuroleptics (Weinberger et al. 1980; Weinberger and Wyatt 1983) and by failure of these agents to reduce the blink rate (Kleinman et al. 1984). On the other hand, there is indication that diminished cerebral serotonin (5-HT) metabolism may underlie the pathophysiology of this schizophrenic subgroup.

At least three groups of investigators (Nyback et al. 1983; Potkin et al. 1983; Losonczy et al. 1986) have reported that schizophrenic patients with cerebral atrophy and enlarged cerebral ventricles had decreased cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) levels as compared with both schizophrenic patients with normal ventricles and normal controls. In addition, Levy et al. (1984) found that schizophrenic patients with enlarged cerebral ventricles had a significantly higher incidence of suicide attempts, which may be related to diminished CSF 5-HIAA concentrations (Ninan et al. 1984). Treatment with the 5-HT2 receptor antagonist, ritanserin, was observed to ameliorate negative symptoms.

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symptoms in patients with enlarged cerebral ventricles (Ceulemans et al. 1985; Gelders et al. 1985). Moreover, the ritanserin-treated patients also showed significant improvement in extrapyramidal symptoms, suggesting that the emergence of abnormal involuntary movements in these schizophrenic patients may be related to impaired 5-HT functions. Indeed, Chase et al. (1970) detected reduced CSF 5-HIAA levels only in those schizophrenic patients who exhibited extrapyramidal symptoms. The reported effect of selective 5-HT₂ antagonists on negative symptoms in patients with enlarged cerebral ventricles, as well as the decreased CSF 5-HIAA levels in these patients, suggests that this type of schizophrenia is associated with 5-HT₂ postsynaptic receptor supersensitivity (Bleich et al. 1988).

The observation that schizophrenic patients with enlarged cerebral ventricles have decreased cerebral 5-HT metabolism (Potkin et al. 1983) and increased blood monoamine oxidase (MAO) (Tachhiki et al. 1984) raises the possibility that these patients may have reduced pineal melatonin secretion. Melatonin is an inhibitor of MAO (Urry and Ellis 1975). In addition, its administration has been shown to increase brain 5-HT concentrations in rats (Anton-Tay et al. 1968), mice (Cotzias et al. 1971), and parkinsonian patients (Anton-Tay 1974), while brain 5-HT concentrations have been reported to decrease in pinealectomized rats (Wendel et al. 1974; Aldegunde et al. 1985). These findings suggest that melatonin stimulates 5-HT synthesis, possibly by enhancing the activity of tryptophan hydroxylase (Aldegunde et al. 1985), and that decreased melatonin secretion may be associated with diminished cerebral 5-HT metabolism.

There is indeed reason to suspect that abnormal pineal melatonin functions are implicated in the pathophysiology of schizophrenia. The proposed melatonin-deficiency hypothesis is based on the following lines of evidence.

1. Pineal glands of schizophrenic patients were reported to show marked sclerosis and gliosis, which could diminish melatonin output and/or induce production of abnormal melatonin compounds (Nieto and Nieto 1987).

2. The activity of pineal hydroxyindole-O-methyltransferase (HIOMT), the final enzyme in melatonin biosynthesis, was found to be reduced by 34 percent in postmortem drug-free schizophrenic patients and tended to increase in neuroleptic-treated patients (Owen et al. 1983).

3. Melatonin may be metabolized into abnormal compounds, which may be etiologically important in the pathogenesis of schizophrenia (McIsaac 1961). A defect in pineal melatonin production due to HIOMT deficiency could lead to formation of the well-known harmala alkaloid 10-methoxyharmaln, an agent that exhibits psychomimetic activity (McIsaac 1961). Since 10-methoxyharmaln and its derivatives are potent MAO inhibitors (Udenfriend et al. 1958; Klein and Weller 1970), 5-HT functions could be disrupted, resulting also in a shunting of accumulated 5-HT into 5-methoxytryptamine and enhanced methoxyharmaln synthesis (Miles and Philbrick 1988). It has also been suggested that the activity of pineal HIOMT is out of phase with its normal substrate (N-acetylsertotonin) and is thus free to produce abnormal methylated compounds, which may be involved in the pathogenesis of the disease (Hartley and Smith 1973). Neuroleptics may ameliorate symptoms of schizophrenia by preventing abnormal transmethylation reactions mediated by pineal HIOMT, the activity of which they block (Hartley et al. 1972).

4. Melatonin stimulates prostaglandin E₁ synthesis (Cardinali 1981), which is deficient in schizophrenia (Horrobin 1979).

5. Pineal extracts have been reported to reduce psychotic behavior in schizophrenic patients (Altschule 1957; Eldred et al. 1961; Bigelow 1974). Interestingly, aqueous pineal extracts that were melatonin-free have been shown to reverse a behavioral abnormality induced by neonatal pinealectomy (Sampson and Bigelow 1971).

6. Abnormalities of glucose metabolism in schizophrenic patients may be corrected by pineal extracts (Altschule 1979).

7. Melatonin output falls rapidly in winter, when there is an excess of schizophrenic births, particularly in negative symptom patients (Opler and Kay 1985).

8. Schizophrenic patients have a characteristic pattern of melanin deposition in the skin, which could be accounted for by melatonin deficiency (Nicolson et al. 1966).

In addition, it has been reported that nocturnal plasma melatonin levels are reduced as compared with normal controls in some (Ferrier et al. 1982; Fanget et al. 1989) but not all (Steiner and Brown 1985) drug-free and neuroleptic-treated chronic schizophrenic patients; however, no mention has been made in the literature regarding the subtype of schizophrenia associated with abnormal melatonin secretion.

The relationship of reduced 5-HT metabolism and melatonin secretion to enlarged cerebral ventricles in schizophrenia remains unknown.
Maurizi (1987) proposed that reduced melatonin secretion may induce a functional block of CSF circulation and thereby contribute to the development of enlarged cerebral ventricles. This hypothesis is supported by observations that 5-HT fibers from the raphe nuclei innervate the choroid plexus (Moskowitz et al. 1979) and that melatonin is involved in regulating the metabolic activity of the choroid plexus (Decker and Quay 1982). Interestingly, a covert transport dysfunction in the choroid plexus has been hypothesized to be a possible cause of schizophrenia (Rudin 1979).

An alternative possibility is that reduced melatonin secretion may contribute ontogenetically to the development of cerebral atrophy in these patients, since pinealectomy is associated with generalized growth retardation and delayed brain maturation in neonatal rats (Csaba and Barath 1975; Relkin and Schneck 1975; Kamback et al. 1982) and with acceleration of the aging process in young rats (Oxenkrug et al. 1984). It is conceivable, therefore, that reduced melatonin secretion from early life may impair CSF circulation as well as brain growth and maturation, ultimately leading to cerebral atrophy and ventricular enlargement. Indeed, negative syndrome schizophrenic patients tend to have more cortical atrophy and enlarged ventricle-brain ratios (Weinberger et al. 1980; Andreasen et al. 1982; Weinberger and Wyatt 1983) as well as greater cognitive developmental deficits than other patients with this diagnosis, which is reflected in disrupted education and poor performance on Piagetian maturational tests (Kay et al. 1986). This schizophrenic subgroup thus tends to show intellectual dysfunction both before the emergence of the active psychosis and after its treatment (Kay, in press).

The involvement of reduced melatonin secretion in the pathophysiology of cerebral atrophy in schizophrenic patients is also suggested by our recent finding of an association between CT scan measures of prefrontal cortical atrophy and pineal calcification (PC) (Sandyk and Kay, in press g). While CT scan measurements of parieto-occipital atrophy and sulcal prominence did not differentiate patients with or without PC, prefrontal cortical atrophy was significantly associated with the presence of PC. Since PC may reflect diminished past secretory activity of the pineal gland (Tapp 1979; Reiter et al. 1980; Trentini et al. 1987), these data imply that reduced melatonin secretion may be involved in the pathophysiology of prefrontal cortical atrophy and be relevant to the presence of frontal lobe dysfunction in the disease.

It has been postulated recently that a "latent" lesion in the prefrontal cortex, revealed only at sexual maturation, interacts with the appropriate genetic predisposition to result in the clinical manifestations of schizophrenia (Weinberger et al. 1986). The role of the pineal gland in determining both the onset of sexual maturation and a possible neurobiological vulnerability for schizophrenic symptoms could explain the well-documented tendency of schizophrenia to present floridly in adolescence, the period of full sexual maturation. If sexual maturation indeed releases a pathologic process, then peripubertal alterations of pineal melatonin functions could play a significant and highly specific role in the pathophysiology of schizophrenia.

The literature suggests that alterations in pineal melatonin functions are closely associated with the process of sexual maturation. Initial evidence for the role of the pineal gland in sexual maturation was derived from observations that pineal tumors may be related to precocious puberty (Kitay 1994). Subsequently, Silman et al. (1979) and Waldhauser et al. (1984) reported a dramatic fall in nocturnal plasma melatonin levels in pubertal children, and it has been suggested that the peripubertal reduction in melatonin secretion may be involved in the initiation of sexual maturation (Sizonenko and Aubert 1986). Since melatonin secretion is chronically diminished in some schizophrenic patients (Ferrier et al. 1982; Fanget et al. 1989), in these cases the peripubertal physiological fall in melatonin secretion may be blunted, ultimately contributing to the emergence of schizophrenic symptoms during adolescence. This hypothesis would accommodate not only the timing of the onset of the illness, but also the impaired premorbidity often encountered and its prediction of both poor outcome and negative symptoms (Pogue-Geile and Harrow 1984; Kay et al. 1986; Kay, in press). It is therefore possible that abnormal peripubertal melatonin secretion may be associated, at least in part, with the emergence of schizophrenic symptoms in a subgroup of patients and that the covariation of prefrontal cortical atrophy with the presence of PC may reflect the peripubertal interaction between abnormal melatonin secretion and prefrontal cortical functions.

The mechanisms by which abnormal peripubertal melatonin secretion may be associated with the emergence of schizophrenia at adolescence remain unknown. There is evidence to suggest that melatonin modulates striatal and limbic dopaminergic activity (Bradbury et al. 1985).
Melatonin-binding sites have been demonstrated in areas rich with dopamine (DA), such as the striatum and limbic system (Zisapel et al. 1988). Zisapel and Laudon (1982) reported in vitro inhibition of DA release induced by electrical field stimulation of rat hypothalamus, while Dubocovich (1983) observed that melatonin inhibited calcium-dependent release of 3H-DA from rabbit retina. Further, melatonin injected into the rat cerebral ventricles has been noted to stimulate prolactin release (Kamberi et al. 1971). These findings indicate that melatonin inhibits limbic dopaminergic activity, raising the possibility that the peripubertal physiological fall of plasma melatonin levels may be related to an episodic increase in dopaminergic activity. In schizophrenia, mesolimbic and mesocortical DA tone may be chronically increased due to diminished melatonin secretion. As a result of the decrease in melatonin secretion during puberty, mesolimbic DA tone may be further augmented, an effect that could be responsible in part for triggering the emergence of schizophrenic symptoms during adolescence.

A subgroup of schizophrenic patients with cerebral atrophy and, specifically, enlarged ventricles are reported to have increased susceptibility to abnormal involuntary movements, including tardive dyskinesia (TD), parkinsonism, and akathisia (Johnstone et al. 1976, 1989; Bartels and Themelis 1983; Albus et al. 1985; Owens et al. 1985; Waddington 1985; Waddington et al. 1985; Kaufman et al. 1986; Hoffman et al. 1987; Sandyk and Kay, in press b, in press h). Owens et al. (1985), Waddington et al. (1985), and Kaufman et al. (1986) reported a significant association between TD and lateral ventricular enlargement in schizophrenia, although other investigators failed to demonstrate such an association (Kolakowska et al. 1986; Swayze et al. 1988). Bartels and Themelis (1983) found that TD covaried significantly with enlargement of the third ventricle, and Luchins et al. (1983) noted that schizophrenic patients with enlarged lateral ventricles required more antiparkinsonian medication when treated with chlorpromazine. These findings suggest that enlarged lateral ventricles may be associated with an increased risk to develop drug-induced parkinsonism. Cerebral ventricular enlargement has also shown positive correlations with the severity of drug-induced parkinsonism in older schizophrenic patients (Hoffman et al. 1987). These observations raise the possibility that reduced melatonin secretion, which seems to be implicated in cerebral atrophy, may also exert a role in the development of abnormal involuntary movements in a subgroup of schizophrenic patients. This proposal is concordant with the following.

1. Greater incidence and severity of abnormal chewing movements have been reported in drug-naive pinealectomized rats as compared with intact rats. In addition, a single administration of intramuscular haloperidol further increased the severity of chewing movements in the pinealectomized rats while melatonin reduced the severity of the abnormal chewing behavior (Sandyk and Fisher 1989). We have suggested, therefore, that the pineal gland may exert a protective effect against the development of TD (Sandyk and Fisher 1988). Increased chewing movements in rats are thought to provide a model for acute drug-induced dystonia (Rupniak et al. 1983, 1985) or withdrawal dyskinesia in humans (Ginne 1987). These findings indicate that reduced melatonin secretion may underlie the development of abnormal involuntary movements and that neuroleptics may induce or facilitate the emergence of involuntary movements in part through interaction with melatonin secretion. Indeed, haloperidol and fluphenazine have been reported to concentrate selectively in the rat pineal gland (Naylor and Olley 1969) and to inhibit pineal HIOMT (Hartley et al. 1972).

2. Depression, which is associated with diminished melatonin secretion (Miles and Philbrick 1988), is a major risk factor for TD and possibly drug-induced parkinsonism. Parkinson's disease, and Meige's disease (idiopathic orofacial dystonia) (Mukherjee et al. 1986b; Kane et al. 1988; Sandyk, in press a; Sandyk and Kay, in press e). Likewise, depressive episodes in bipolar patients covary significantly with the exacerbation of TD (Cutler et al. 1981; Weiner and Werner 1982).

3. Mania, which is associated with increased melatonin secretion (Lewy et al. 1981; Miles and Philbrick 1988), is conversely related to an attenuation in the severity of TD in bipolar patients (Cutler et al. 1981; Weiner and Werner 1982). Moreover, TD seemed to be absent in a sample of neuroleptic-treated unipolar manic patients (Mukherjee et al. 1986b).

4. Aging, which is associated with reduced melatonin secretion (Nair et al. 1986; Sack et al. 1986; Thomas and Miles 1989), is a major risk factor for both TD and drug-induced parkinsonism (Smith and Baldessarini 1980; Kane et al. 1988). In addition, 24-hour melatonin secretion is significantly lower in patients with Alzheimer's disease than in age-matched healthy subjects (Nair et al. 1986). There is an increased prevalence of

5. It has recently been observed that the presence of TD (Sandyk, in press c; Sandyk and Kay, in press f), of drug-induced dystonic movements (Sandyk and Kay, in press a) and of drug-induced parkinsonism (Sandyk, in press b) was significantly related to the presence of PC and, specifically, to pathologically enlarged calcified pineal glands on CT scan.

6. There is an increased prevalence of diabetes mellitus in patients with TD (Mukherjee et al. 1986a), Parkinson's disease (Lipman et al. 1974), and drug-induced parkinsonism (Sandyk and Kay, in press c in press d). Since experimentally induced hyperglycemia augments the development of neuroleptic-induced dyskinesias in rats (Sandyk 1990), it is possible that impaired glucose tolerance is associated with an increased risk of TD. Experimentally induced hyperglycemia is associated with diminished melatonin secretion in rats (Pang et al. 1985), and pineal weight is decreased in diabetic subjects (Trentini et al. 1987). It is conceivable, therefore, that the increased prevalence of TD and parkinsonism in diabetic patients may in part be related to reduced melatonin secretion (Mukherjee et al. 1989).

The hypothesis that reduced melatonin secretion exerts a role in the pathophysiology of a subgroup of schizophrenic patients has several clinical implications.

1. Subnormal plasma melatonin levels may be markers of a subgroup of schizophrenic patients characterized by cerebral atrophy, negative symptoms, and impaired cognitive functions.

2. Subnormal melatonin plasma levels may serve as a marker of genetic susceptibility to this subtype of schizophrenia.

3. Subnormal plasma melatonin levels may be markers of vulnerability to drug-induced movement disorders. The presence of PC and, in particular, of pathologically enlarged PC (i.e., > 1 cm in diameter) on CT scan may signify a special risk for developing TD, parkinsonism, and drug-induced dystonia.

4. Subnormal plasma melatonin levels may predict poor response to neuroleptics, and administration of melatonin or its precursors and cofactors (L-tryptophan, pyridoxine, folic acid) may possibly enhance the antipsychotic efficacy of neuroleptics in this subgroup of schizophrenic patients, in part by "down" regulating the 5-HT2 receptors.

5. Coadministration of neuroleptics with melatonin or melatonin-release-enhancing agents (i.e., 5-methoxyxpsoralen/Souetre et al. 1988) may decrease the risk of developing drug-induced abnormal involuntary movements.

In summary, on the basis of recent converging paths of research, we propose that reduced melatonin secretion may be involved in the pathophysiology of schizophrenia for a subgroup of patients characterized by cerebral atrophy and enlarged ventricular size, cognitive developmental failure and impaired psychosexual maturation, onset of manifest illness at pubescence, presence of negative symptoms and relatively poor response to classic neuroleptics, and increased susceptibility to developing abnormal involuntary movements. This hypothesis carries specific predictions and implications that are amenable to empirical testing; this is the focus of our forthcoming research.

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ventricular enlargement and suicide


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