Neuroendocrinology Letters ISSN 0172–780X

ORIGINAL ARTICLE

A study of light/dark rhythm of melatonin in relation to cortisol and prolactin secretion in schizophrenia

Daniele Viganò,[1] Paolo Lissoni,[2] Franco Rovelli,[2] Maria Grazia Roselli,[2] Fabio Malugani,[2] Carlo Gavazzeni,[1] Ario Conti[3] & George Maestroni[3]

1. Division of Psychiatry, S.Gerardo Hospital, Monza (Milan), Italy.
2. Division of Radiation Oncology, S.Gerardo Hospital, Monza (Milan), Italy.
3. Institute of Pathology, Locarno, Switzerland.

Correspondence to: Dr. Paolo Lissoni
Unità Operativa di Radioterapia Oncologica
Ospedale S. Gerardo dei Tintori
20052 Monza (Milan), Italy.
FAX +39 039 233 2284

Submitted: *April 10, 2001*
Accepted: *April 12, 2001*

Key words: **cortisol; melatonin; pineal gland; prolactin; schizophrenia**

*Neuroendocrinology Letters 2001; **22**:137–141 pii: NEL220201A08 Copyright © Neuroendocrinology Letters 2001*

Abstract

OBJECTIVES: Recent studies have suggested the involvement of the pineal gland and its main hormone melatonin (MLT) in the pathogenesis of psychiatric disturbances, namely the depressive syndrome. In contrast, the behavior of MLT secretion in schizophrenia is still controversial.

MATERIAL & METHODS: The present study was carried out to analyze light/dark rhythm of MLT secretion in relation to that of cortisol and prolactin (PRL) in schizophrenic patients. The study included 13 schizophrenic patients, 8 of whom were untreated, while the other 5 patients were on neuroleptic therapy. Serum levels of MLT, PRL and cortisol were measured by RIA on venous blood samples collected at 8 A.M., 12 A.M., 8 P.M. and 1 A.M. The control group consisted of 20 age-matched healthy subjects.

RESULTS: A physiological nocturnal increase in MLT levels occurred in 6/13 patients, whereas the other 7 patients showed an abnormally low MLT peak during the night. Moreover, both light and night mean levels of MLT were significantly lower in patients than in controls. In addition, mean nocturnal levels of MLT were significantly lower in chronic patients than in those evaluated at the onset of disease. Cortisol rhythm was normal in 11/13 patients, whereas PRL levels were abnormally high in 10/13 patients.

CONCLUSIONS: This preliminary study would suggest that schizophrenia may be associated with a diminished secretion of MLT from the pineal gland, and pineal deficiency would be more evident in the chronic disease. Finally, pineal alterations have appeared to be associated with an altered secretion of PRL and cortisol, by suggesting that the schizophrenic disease may be characterized by marked neuroendocrine disturbances, whose physio-pathological and prognostic significance needs to be established by successive clinical investigations.

Introduction

After the historical mistake of the interpretation of the pineal gland as a non-functioning organ, the recent advances in the knowledge of the psychoneuroendocrinology have shown that the pineal gland is a multifunctional neuroendocrine organ, able to modulate almost all biological systems, in relation to environmental and emotional stimulations through the circadian release of indole hormones, among them melatonin (MLT) would represent the most investigated pineal substance [1, 2]. MLT has been proven to influence psychoneuroendocrine, immune and vascular activities by acting on specific cell surface and nuclear melatoninergic receptors [3], as well as by modulating the expression of other receptors for neurotransmitters and neuropeptides.

In physiological conditions, MLT secretion increases during the dark period of the day, resulting in a well defined circadian rhythm [1–4], which plays a fundamental role in maintaining other circadian biological variations, including brain opioid tone and neurotransmitter contents, as well as the immune functions [5].

An altered pineal rhythm of MLT secretion, mainly consisting of a lack of the physiological night increase, has been observed in several severe human illnesses, including advanced cancer [6], ischemic stroke [7] and depression [3]. Therefore, because of its importance as a regulator of the biological systems, the evidence of a lack of MLT circadian rhythm would constitute a non-specific neurobiological marker of severe systemic human diseases.

As far as psychiatric disorders are concerned, even though controversial results exist, it is commonly accepted that the depressive syndrome may at least be associated with a reduced MLT night secretion [8, 9], which could play a role in determining depression-associated enhanced activity of the pituitary-adrenal axis. On the contrary, the possible association between pineal alterations and schizophrenia has been less investigated. Preliminary evidences would suggest that the pineal might be involved in determining at least some schizophrenia-related symptoms, such as hallucinations [10]. In fact, pineal obtained from deceased schizophrenic patients have been shown to be able to transform MLT into 10-methoxy-armalane [10], which may induce important psychedelic effects, because of its chemical structure, similar to that of the hallucinogenic agent armaline. Moreover, several hallucinogens, e.g. mescaline, armaline, dimethyl-tryptamine [11] and cannabinoid compounds [12] have been proven to stimulate MLT secretion by activating the pineal enzyme hydroxyindole-O-methyl-transferase (HIOXT), which is the last enzyme involved in the biosynthesis of MLT from N-acetylserotonin. In addition, the acute intravenous injection of highly pharmacological doses of MLT has appeared to re-induce the hallucinatory symptomatology for some days in schizophrenic patients clinically free from psychotic symptoms [13]. These experimental evidences would suggest an enhanced MLT release in schizophrenia, since MLT and other less known psychomimetic pineal substances are probably involved in the biochemistry of the status of consciousness [3]. Unfortunately, preliminary clinical studies would seem to exclude a pineal hyperfunction in schizophrenic patients, who in contrast seem to be characterized by a reduced pineal function, at least in terms of MLT circadian secretion [14]. In fact, abnormally low nocturnal blood concentrations of MLT have been observed in chronic schizophrenic patients [14]. This evidence has not been confirmed by other authors [15], who described normal blood levels of MLT in schizophrenia. The different subtypes of schizophrenia and stages of disease, as well as the possible influence of treatments, could be the variables responsible for the controversial results referred by the various authors in literature. Therefore, a dysregulation of the pineal gland rather than a reduced endocrine activity could be involved in the pathogenesis of at least some schizophrenia-related symptoms. The present study was performed, as an attempt to better investigate MLT circadian rhythm in a group of schizophrenic patients, in relation to that of two other hormones, whose secretion is often altered in psychiatric diseases, e.g. cortisol and prolactin (PRL).

Materials and methods

The study included 13 consecutive schizophrenic patients (M/F: 6/7; median age: 26 years, range 20–37 years), who were admitted at Psychiatric Division of the Hospital of Monza. The diagnosis of schizophrenia was made according to DSM-III-R. Eight patients were evaluated at the onset of disease and they were free from therapy. The other five were chronic patients and they were on treatment with neuroleptic drugs at the time of the study. The control group consisted of 20 age- and sex-matched healthy subjects. To evaluate MLT circadian secretion, venous blood samples were collected at 8 A.M., 12 A.M., 8 P.M. and at 1 A.M. Cortisol and PRL were also evaluated in the same blood samples. Both patients and healthy controls followed a normal wake-sleep rhythm during the study. Samples were collected through an indwelling catheter inserted in an antecubital vein. The night samples were drawn, after at least 3 hours of complete darkness, by using a red light during the blood collection, representing the only light that does not inhibit MLT secretion.

Serum samples were obtained by centrifugation and stored at –70°C until assayed. Samples were measured in duplicate within 30 days from the blood sampling. Serum levels of MLT, PRL and cortisol were measured with the double antibody RIA method by using commercial kits, and results were statistically evaluated by the chi-square test, the Student's T test and the analysis of variance at multiple time points, as appropriate.

Results

As expected, night mean serum levels of MLT observed in the healthy controls were significantly higher than those seen during the light period of the day ($p < 0.001$). Moreover, all healthy subjects showed night concentrations of MLT at least higher than 30 pg/ml. A normal nocturnal increase in MLT levels occurred in 6 patients only, whereas the remaining 7/13 (54%) patients showed an abnormally low MLT night increase. Moreover, MLT mean serum levels observed in schizophrenic patients were lower than in control subjects over the whole 24-hour daily period, and this difference was statistically significant at 1.00 A.M. ($p < 0.001$) and at 8.00 A.M. ($p < 0.05$). In addition, schizophrenic patients evaluated at the onset of the psychotic symptomatology in a therapy-free period showed mean nocturnal levels of MLT significantly higher with respect to those seen in the chronic patients ($p < 0.05$). Daily mean concentrations of MLT observed in healthy subjects and in schizophrenic patients are illustrated in Fig. 1, whereas Fig. 2 shows those found in chronic patients and in patients evaluated at the onset of disease.

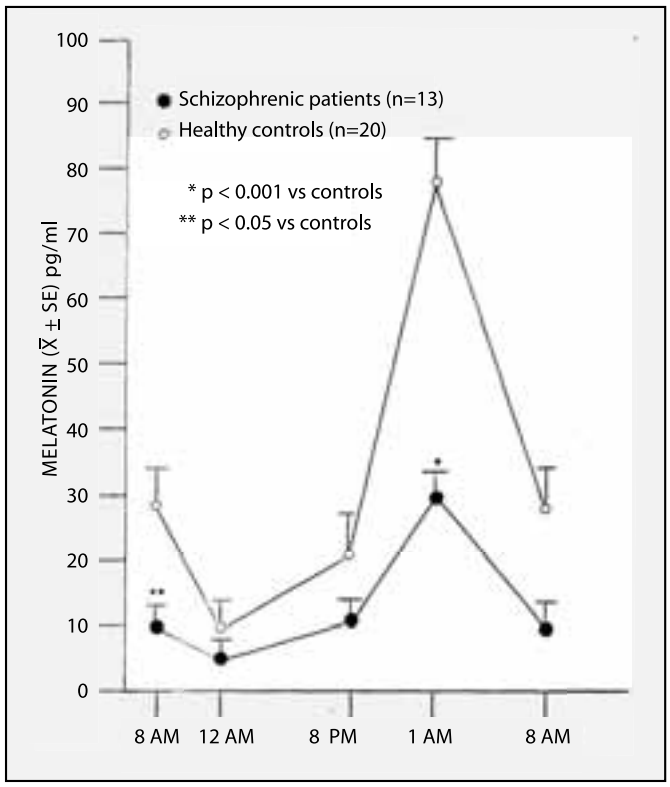

Fig. 1. Circadian serum levels of melatonin (mean ± SE) in healthy controls and in schizophrenic patients.

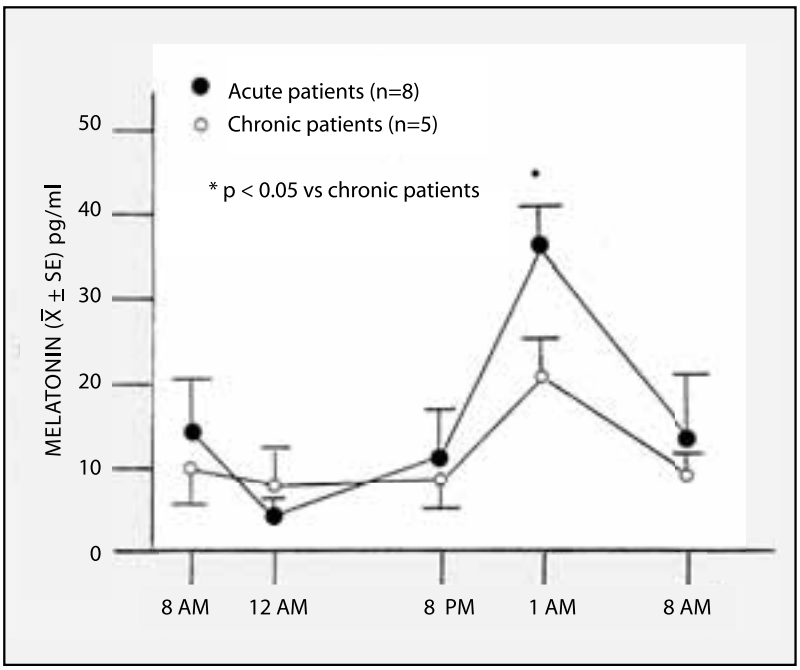

Fig. 2. Circadian serum levels of melatonin (mean ± SE) observed in chronic schizophrenic patients and in those evaluated at the onset of disease.

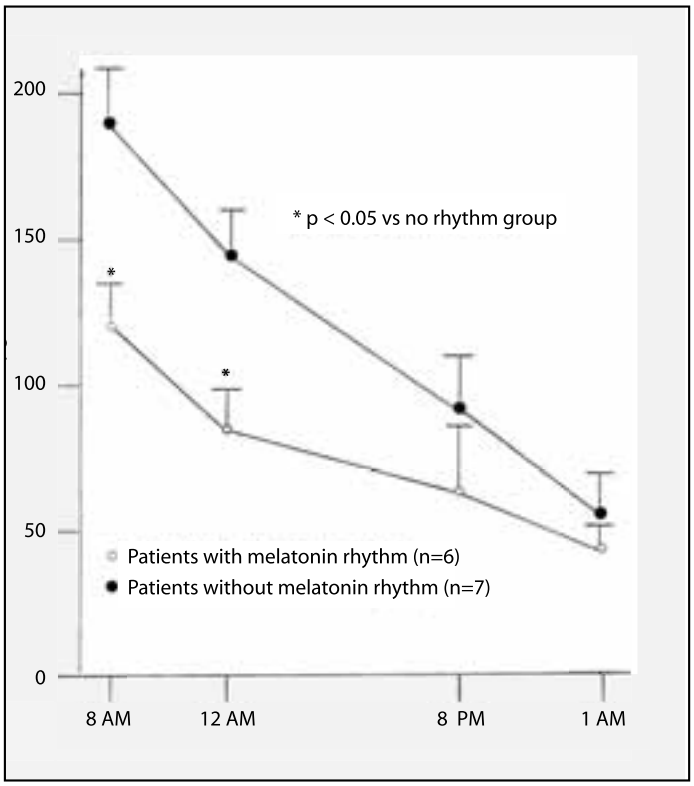

Fig. 3. Circadian serum levels of cortisol (mean ± SE) in schizophrenic patients with or without a physiological light/dark rhythm of melatonin.

A normal cortisol circadian secretion, with the highest concentrations during the morning and the lowest ones during the night, was observed in 11/13 patients, whereas 2 patients only (15%) had an altered cortisol rhythmicity. In addition, as illustrated in Fig. 3, mean levels of cortisol observed at 8.00 A.M. and at noon were significantly higher in schizophrenic patients who had no MLT rhythm than in those showing a normal MLT nocturnal increase ($p < 0.05$). Finally, PRL serum concentrations were within the normal range only in 3 patients, whereas they were abnormally high in 10/13 (76%) patients. More in details, PRL was elevated in all 5/5 chronic patients and in 5/8 acute patients. This difference was not significant. In addition, as reported in Table 1, mean levels of PRL were higher in the group of patients with a lack of MLT rhythm than in those showing a normal light/dark MLT circadian secretion, without, however, statistically significant differences.

Discussion

Although limited to a small number of patients, this study shows that schizophrenia is associated with a diminished production of the pineal hormone MLT, particularly during the night, which represents the daily period of its physiological increase [1–4]. Therefore, in agreement with the results reported by Fanget et al. [14], this study would suggest the occurrence of a pineal hypofunction in schizophrenia. The existence of a reduced MLT secretion as a neurobiochemical alteration, at least in part responsible for schizophrenic symptoms, is also suggested by the evidence that effective drugs in the treatment of the schizophrenic symptomatology, such as the neuroleptic drug haloperidol, have appeared to stimulate MLT secretion [16]. Moreover, this study, by showing lower nocturnal levels of MLT in chronic schizophrenic patients than in those evaluated at the onset

Table 1. Circadian serum levels of PRL (mean ± SE) in schizophrenic patients with or without normal circadian rhythm of melatonin.

patients		PRL (ng/mL)			
		8 AM	12 AM	8 PM	1 AM
normal melatonin rhythm	6	27 ± 8	33 ± 12	34 ± 10	49 ± 12
no melatonin rhythm	7	35 ± 7	44 ± 10	35 ± 7	54 ± 10

of the psychotic symptomatology, would suggest that the clinical course of schizophrenia may be characterized by a progressive and worsening pineal damage. However, longitudinal studies, by monitoring patients during the clinical course of disease, will be required to confirm schizophrenia-related progressive pineal hypofunction, at least in terms of MLT nocturnal production. The controversial results described in literature about MLT production in schizophrenia could depend on the possible changes in the pineal function, in relation to the different stages of disease.

Finally, the evidence of higher daily levels of cortisol in schizophrenic patients, who showed no MLT light/dark rhythm than in those with normal circadian secretion, as observed in the present study, could suggest a possible involvement of the pineal in determining psychiatric disease-associated adrenal dysfunctions, as well as the existence of different types of pineal-adrenal interactions in the biochemistry of the schizophrenic process. At present, it remains to be established whether there is a relation between pineal-adrenal connections and clinical and prognostic characteristics of schizophrenia. In contrast, PRL secretion does not seem to present different patterns in relation to that of MLT.

Obviously, MLT is only one of the pineal hormones possibly involved in the pathogenesis of schizophrenia. Other pineal indoles, also provided by evident effects on the psychoemotional status and by potential psychomimetic activity, such as 5-methoxytryptophol and 5-methoxytryptamine, could also show altered secretions and be involved in the generation of psychotic symptoms. In any case, the evidence of a reduced MLT night secretion particularly in chronic schizophrenic patients would justify randomized therapeutic studies with neuroleptics alone, such as haloperidol, versus neuroleptics plus MLT and/or other pineal indoles.

REFERENCES

1 Axelrod J. The pineal gland: a neurochemícal transducer. Science 1974; **184**:1341–1348.
2 Arendt J. Melatonin. Clin Endocrinol 1988; **29**:205–229.
3 Brzezinsky A. Melatonin in humans. N Engl J Med 1997; **336**:186–195.
4 Attanasio A, Borrelli P, Gupta D. Circadian rhythms in serum melatonin from infancy to adolescence. J Clin Endocrinol Metab 1985; **61**:388–390.
5 Régelson W, Pierpaoli W. Melatonin: a rediscovered antitumor hormone? Cancer Invest 1987; **5**:379–385.
6 Bartsch C, Bartsch H, Lippert TH. The pineal gland and cancer: facts, hypotheses and perspectives. Cancer J 1992; **5**:194–199.
7 Fiorina P, Lattuada G, Ponari O, Silvestrini C, Dall'Aglio P. Impaired nocturnal melatonin excretion and changes of immunological status in ischemic stroke patients. Lancet 1996; **347**:692–693.
8 Branchey L, Weinberg U, Branchey M, Linkowski P, Mendelewicz J. Simultaneous study of 24-hour pattern of melatonin and cortisol secretion in depressed patients. Neuropsychobiology 1982; **8**:225–232.
9 Grof E, Grof P, Brown GM, Arato M, Lane J. Investigations of melatonin secretion in man. Prog Neuropsychopharmacol Biol Psychiat 1985; **9**:609–612.
10 McIsaac WM. A biochemical concept of mental disease. Postgrad Med 1961; **30**:111–118.
11 Lynch HJ, Wang P, Wurtman RJ. Increase in rat pineal melatonin content following L-dopa administration. Life Sci 1973; **12**:145–151.
12 Lissoni P, Resentini M, Mauri R, Esposti D, Esposti G, Rossi D, Legname G, Fraschini F. Effects of tetrahydrocannabinol on melatonin secretion in man. Horm Metab Res 1986; **18**: 77–78.
13 Altschule MD. Some effects of aqueous extracts of acetone extracts of acetone dried been pineal substance in chronic schizophrenia. N Engl J Med 1957; **257**:919–922.
14 Fanget F, Claustrat B, Dalery C, Brun J, Terra JL, Marie-Cardin M, Guyotat J. Nocturnal plasma melatonin levels in schizophrenic patients. Biol Psychiat 1989; **25**:499–501.
15 Beckmann H, Wetterberg L, Gattaz WF. Melatonin immunoreactivity in cerebrospinal fluid of schizophrenic patients and healthy controls. Psychiat Res 1984; **11**:107–110.
16 Gaffori O, Geffard M, Van Ree JM. Des-tyr-gamma-endorphin and haloperidol increase pineal melatonin levels in rat. Peptides 1983; **4**:493–495.