Psychological Medicine, 1987, **17**, 817–820
Printed in Great Britain

EDITORIAL

The pineal and psychiatry: still fumbling in the dark?[1]

Since the identification of the pineal as an endocrine organ there have been numerous attempts to link alterations in the function of the gland with pathological states (Mullen & Silman, 1977). Unfortunately the role of the pineal in normal human physiology is still unknown, although there are suggestions that it may be involved in the control of sexual development (Waldhauser *et al.* 1984).

MEASUREMENT OF MELATONIN

While the pineal elaborates a number of hormones, melatonin remains the focus of interest. Human investigations have been greatly aided by the development by Josephine Arendt and her colleagues of a sensitive and specific radioimmunoassay for melatonin in plasma (Arendt & Wilkinson, 1979). Recently, the assay has been simplified so that plasma extraction is no longer necessary (Fraser *et al.* 1983*a*). Results from this assay compare well with the reference method of gas chromatography-mass spectrometry (Fraser *et al.* 1983*b*).

Using such validated assays it has been established beyond doubt that in man there is a circadian rhythm in plasma melatonin; peak concentrations occur at night between 2.00 and 4.00 a.m., while levels in the day time are much lower (< 10 pg/ml), (Arendt *et al.* 1982). Investigations in normal subjects reporting day time levels of melatonin consistently above this value should be received with caution. There is considerable variation between individuals in the amount of melatonin secreted each night but the quantity secreted by an individual is fairly consistent. It has been shown that the melatonin concentration in a single blood sample taken at midnight correlates highly with both the peak nocturnal melatonin level and the total night time secretion (Arendt *et al.* 1982; Arato *et al.* 1985); this finding can considerably simplify study design. Urinary estimation of the melatonin metabolite, 6-hydroxymelatonin sulphate (Arendt, 1986), may also obviate the need for repeated blood sampling throughout the night.

CONTROL OF MELATONIN SECRETION

Animal studies have shown that the circadian rhythm of melatonin secretion is controlled by an endogenous 'pacemaker' in the suprachiasmatic nucleus in the hypothalamus (Moore, 1978). Through a multi-synaptic pathway the pacemaker alters the amount of noradrenaline released from the pre-junctional sympathetic nerve endings which synapse with pineal cells. At night there is a large and sustained increase in noradrenaline release which correlates with the elevation of pineal and plasma melatonin (Axelrod, 1974).

In both animals (Axelrod, 1974) and man (Vaughan *et al.* 1976) the post-junctional noradrenergic receptors on pineal cells are of the β-adrenergic type. A single 100 mg dose of the β_1-selective β-adrenoceptor antagonist, atenolol, markedly reduces midnight melatonin levels in normal subjects (Cowen *et al.* 1983*a*), suggesting that these receptors are of the β_1-subtype. In patients receiving long-term antihypertensive treatment with β-adrenoceptor antagonists, nocturnal melatonin levels are persistently suppressed (Cowen *et al.* 1985*a*).

In animals, it has been apparent for some time that both artificial and natural light can suppress plasma melatonin levels (Axelrod, 1974) via a neuronal pathway linking the retina to the

[1] Address for correspondence: Dr P. J. Cowen, University Department of Psychiatry and MRC Unit of Clinical Pharmacology, Research Unit, Littlemore Hospital, Littlemore, Oxford OX4 4XN.

suprachiasmatic nucleus (Moore, 1978). Thus the amount of melatonin secreted depends to some extent on the prevailing day length. Since alteration in day length is a prominent signal of seasonal change, it is possible that variations in plasma melatonin secretion could act as a trigger to the induction of seasonally linked behaviours. Indeed, this has been shown to be the case for seasonal breeding in ewes (Arendt *et al.* 1983).

Based on studies using domestic artificial light, it was previously believed that the secretion of melatonin in man was not altered by changes in environmental lighting. However, in an ingenious study, Lewy and his colleagues showed that very bright artificial light (> 2500 lux), of an intensity similar to that of natural daylight, could suppress nocturnal melatonin levels in human subjects (Lewy *et al.* 1980).

From the foregoing it will be apparent that measurement of melatonin may be of interest in psychiatric conditions which have a seasonal occurrence. In addition, melatonin concentrations could provide an index of noradrenergic transmission, and of the timing of circadian rhythms. These three issues are relevant to the field of affective disorders, where much recent pineal research has concentrated.

DEPRESSIVE ILLNESS

Three recent studies in drug-free depressed patients have found decreased nocturnal melatonin levels, though in one investigation the abnormality was restricted to subjects with the melancholic subtype of DSM-III major depression (Claustrat *et al.* 1984; Nair *et al.* 1984; Brown *et al.* 1985). A fourth study where patients continued to receive psychotropic medication also found reduced melatonin concentration in depressed patients, but only in those who were non-suppressors in the dexamethasone test (Wetterberg, 1983). It is not clear that all these investigations were controlled adequately for potentially confounding variables such as age (Nair *et al.* 1986) and stage of the menstrual cycle (Webley & Leidenberger, 1986); it is therefore not altogether surprising that a recent controlled study in depressed patients has found no decrease in nocturnal melatonin levels (Thompson *et al.* 1987). It appears that further work is needed to resolve the matter.

If melatonin secretion were to be reduced in depressive illness it might be due to decreased noradrenergic transmission; however, other explanations would be possible. In the studies mentioned above there was no evidence for a consistent change in the timing of circadian rhythms in depressed patients.

ANTIDEPRESSANT DRUG TREATMENT

Longer-term (1–3 weeks) administration to rats of many different antidepressant treatments, including tricyclic antidepressants (TCAs), electroconvulsive shock and monoamine oxidase inhibitors (MAOIs), produces a reduction in the number of post-synaptic β-adrenoceptors in forebrain regions (Sellinger-Barnett *et al.* 1980; Pandey *et al.* 1979). This finding has led to the suggestion that the therapeutic effects of antidepressant treatment might be due to a slowly evolving decrease in transmission through β-adrenergic synapses (Sulser, 1979). The post-junctional β-adrenoceptors in the pineal resemble pharmacologically those in the forebrain, and in rats treatment with TCAs and MAOIs produces identical changes in the β-adrenoceptors in the two tissues (Moyer *et al.* 1981).

In rodents the effects of TCAs to decrease pineal β-adrenoceptor number is associated with a corresponding reduction in the amount of melatonin produced (Heydorn *et al.* 1982; Cowen *et al.* 1983*b*). Thus measurement of melatonin should provide information about alterations in β-adrenergic transmission during antidepressant treatment in human subjects.

In normal subjects, acute TCA administration elevates nocturnal plasma melatonin (Cowen *et al.* 1985*b*; Franey *et al.* 1986). This probably represents increased pineal noradrenergic transmission due to inhibition by the TCA of noradrenaline uptake into pineal prejunctional terminals. After three weeks' continuous treatment, however, melatonin levels have returned to baseline values (Cowen *et al.* 1985*b*; Thompson *et al.* 1985). One explanation for this finding is that in normal subjects TCA treatment does induce a slow decrease in pineal β-adrenoceptor sensitivity, but that

this decrease represents a homeostatic response which restores pineal noradrenergic transmission to normal in the presence of the TCA.

In depressed patients the effects of antidepressant treatment have been less consistent (Frazer *et al.* 1986) but it is possible that plasma melatonin levels are persistently elevated by TCA (Thompson *et al.* 1985; Sack & Lewy, 1986) and MAOI administration (Murphy *et al.* 1986). This could indicate interesting differences in homeostatic responses between depressed patients and normal subjects. At any event it appears that if plasma melatonin secretion is a valid model of noradrenergic function, antidepressant treatments in man do not decrease transmission through β-adrenergic synapses; indeed, in depressed patients an increase in transmission may occur.

SEASONAL AFFECTIVE DISORDER

Recently Rosenthal and his colleagues described a group of patients in whom a recurrent depressive disorder occurs in the autumn and winter months (Rosenthal *et al.* 1984). The term Seasonal Affective Disorder (SAD) was coined for this condition. Based on the hypothesis that the depressive symptoms in these patients might be caused by a peculiar sensitivity to decreasing day length, therapeutic trials were conducted in which the day length was extended using bright artificial light both late at night and early in the morning (Rosenthal *et al.* 1984). These measures had a striking antidepressant effect which was not apparent when ordinary domestic lighting was substituted for the bright light. It was suggested that the antidepressant effect of bright light could be due to its ability to suppress plasma melatonin, perhaps thereby reproducing a pattern of secretion similar to that obtaining during the summer months (Rosenthal *et al.* 1984).

It now appears that this attractive hypothesis is untenable. Administration of atenolol in doses which suppress plasma melatonin does not alleviate depressive symptoms in subjects with SAD (Rosenthal *et al.* 1986). More critically, two recent studies have shown that bright light given in the middle of the day, when melatonin levels are low, is also effective in treating SAD (Wehr *et al.* 1986; Thompson, personal communication). Thus, if bright light has a specific antidepressant effect its mechanism is not due to alterations in plasma melatonin.

There is in fact some evidence that patients with classical manic depressive illness may be unusually sensitive to the suppressant effect of light on melatonin secretion. Lewy and his colleagues reported that in euthymic bipolar patients, nocturnal melatonin could be suppressed by light of an intensity (500 lux) which has little effect on the melatonin levels of normal subjects (Lewy *et al.* 1985). The mechanism of this intriguing finding is unclear but it could represent an abnormal sensitivity of the suprachiasmatic nucleus to the effects of light.

MELATONIN AND CIRCADIAN RHYTHMS

In addition to its role in seasonal behaviours, animal studies have indicated that melatonin may be involved in the synchronization of circadian rhythms (Redman *et al.* 1983). This has led to the interesting suggestion that melatonin may be a useful therapeutic agent where sudden environmental change causes symptoms associated with circadian rhythm disruption. A preliminary study has shown that melatonin may reduce the symptoms of jet lag (Arendt *et al.* 1986); this pharmacological use of melatonin, if confirmed, could have many applications.

P. M. GRASBY AND P. J. COWEN

P.M.G. was supported by the Wellcome Trust.

REFERENCES

Arato, M., Grof, E., Grof, P., Laszlo, I. & Brown, G. M. (1985). In *The Pineal Gland: Endocrine Aspects* (ed. G. M. Brown & S. D. Wainwright), pp. 277–282. Pergamon Press: Oxford.

Arendt, J. (1986). Assay of melatonin and its metabolites: results in normal and unusual environments. *Journal of Neural Transmission* Suppl. 21, 11–33.

Arendt, J. & Wilkinson, M. (1979). In *Methods of Hormone Radioimmunoassay* (ed. B. Jaffe & H. Behrman), pp. 101–119. Academic Press: New York.

Arendt, J., Hampton, S., English, J., Kwasowski, P. & Marks, V. (1982). 24-hour profiles of melatonin, cortisol, insulin, C-peptide and GIP following a meal and subsequent fasting. *Clinical Endocrinology* **16**, 89–95.

Arendt, J., Symons, A. M., Laud, C. A. & Pryde, S. J. (1983).

Melatonin can induce early onset of the breeding season in ewes. *Journal of Endocrinology* **97**, 395–400

Arendt, J., Aldhous, M. & Marks, V. (1986). Alleviation of jet lag by melatonin: preliminary results of controlled double blind trial. *British Medical Journal* **292**, 1170.

Axelrod, J. (1974). The pineal gland: a neurochemical transducer. *Science* **184**, 1341–1348.

Brown, R., Kocsis, J. H., Caroff, S., Amsterdam, J., Winokur, A., Stokes, P. E. & Frazer, A. (1985). Differences in nocturnal melatonin secretion between melancholic depressed patients and control subjects. *American Journal of Psychiatry* **142**, 811–816.

Claustrat, B., Chazot, G., Brun, J., Jordan, D. & Sassolas, G. (1984). A chronobiological study of melatonin and cortisol secretion in depressed subjects: plasma melatonin, a biochemical marker in major depression. *Biological Psychiatry* **19**, 1215–1229.

Cowen, P. J., Fraser, S., Sammons, R. & Green, A. R. (1983*a*). Atenolol reduces plasma melatonin concentration in man. *British Journal of Clinical Pharmacology* **15**, 579–581.

Cowen, P. J., Fraser, S., Grahame-Smith, D. G , Green, A. R. & Stanford, C. (1983*b*). The effect of chronic antidepressant administration on beta-adrenoceptor function of the rat pineal. *British Journal of Pharmacology* **78**, 89–96

Cowen, P. J., Bevan, J. S., Gosden, B. & Elliott, S. A. (1985*a*). Treatment with β-adrenoceptor blockers reduces plasma melatonin concentration. *British Journal of Clinical Pharmacology* **19**, 258–260.

Cowen, P. J., Green, A. R., Grahame-Smith, D. G. & Braddock, L. E. (1985*b*). Plasma melatonin during desmethylimipramine treatment: evidence for changes in noradrenergic transmission. *British Journal of Clinical Pharmacology* **19**, 799–805.

Franey, C., Aldhous, M., Burton, S , Checkley, S. & Arendt, J. (1986). Acute treatment with desipramine stimulates melatonin and 6-sulphatoxy melatonin production in man. *British Journal of Clinical Pharmacology* **22**, 73–79.

Fraser, S., Cowen, P , Franklin, M., Franey, C. & Arendt, J. (1983*a*). Direct radioimmunoassay for melatonin in plasma. *Clinical Chemistry* **29**, 396–397.

Fraser, S., Cowen, P., Franklin, M. & Lewy, A. J. (1983*b*). Direct radioimmunoassay and gas chromatography-mass spectrometry compared for determination of melatonin in plasma. *Clinical Chemistry* **29**, 1703–1704.

Frazer, A., Brown, R., Kocsis, J., Caroff, S., Amsterdam, J , Winokur, A., Sweeney, J. & Stokes, P. (1986). Patterns of melatonin rhythms in depression. *Journal of Neural Transmission* Suppl. 21, 269–290.

Heydorn, W. E., Brunswick, D. J. & Frazer, A. (1982). Effect of treatment of rats with antidepressants on melatonin concentrations in the pineal gland and serum. *Journal of Pharmacology and Experimental Therapeutics* **222**, 534–544.

Lewy, A. J., Wehr, T. A., Goodwin, F. K., Newsome, D. A. & Markey, S. P. (1980). Light suppresses melatonin secretion in humans. *Science* **210**, 1267–1269.

Lewy, A. J., Nurnberger, J. I., Wehr, T. A., Pack, D., Becker, L. E., Powell, R. L. & Newsome, D. A. (1985). Supersensitivity to light: possible trait marker for manic depressive illness. *American Journal of Psychiatry* **142**, 725–727.

Moore, R. Y. (1978). In *Frontiers in Neuroendocrinology* (ed. W. F. Ganong & L. Martin), vol. 5, pp. 185–206. Raven Press: New York.

Moyer, J. A., Greenberg, L. H., Frazer, A. & Weiss, B. (1981). Subsensitivity of the beta-adrenergic receptor linked adenylate cyclase system of rat pineal gland following repeated treatment with desmethylimipramine and nialamide. *Molecular Pharmacology* **19**, 187–193.

Mullen, P. & Silman, R. (1977). The pineal and psychiatry: a review. *Psychological Medicine* **7**, 407–417.

Murphy, D. L., Tamarkin, L., Sunderland, T., Garrick, N. A. & Cohen, R. M. (1986). Human plasma melatonin is elevated during treatment with the monoamine oxidase inhibitors clorgyline and tranylcypromine but not deprenyl. *Psychiatry Research* **17**, 119–127.

Nair, N. P. V., Hariharasubramanian, N. & Pilapil, C. (1984). Circadian rhythm of plasma melatonin in endogenous depression. *Progress Neuro-Psychopharmacology and Biological Psychiatry* **8**, 715–718.

Nair, N. P. V., Hariharasubramanian, N., Pilapil, C., Isaac, I. & Thavundayil, J. X. (1986). Plasma melatonin – an index of brain aging in humans? *Biological Psychiatry* **21**, 141–150.

Pandey, G. N., Heinze, W. J., Brown, B. D. & Davis, J. M. (1979). Electroconvulsive shock treatment decreases beta-adrenergic sensitivity in rat brain. *Nature* **280**, 234–235.

Redman, J., Armstrong, S. & Ng, K. T. (1983). Free running activity rhythms in the rat: entertainment by melatonin. *Science* **219**, 1089–1091.

Rosenthal, N. E., Sack, D. A., Gillin, J. C., Lewy, A. J., Goodwin, F. K., Davenport, Y., Mueller, P. S., Newsome, D. A. & Wehr, T. A. (1984). Seasonal affective disorder. *Archives of General Psychiatry* **41**, 72–80.

Rosenthal, N. E., Sack, D. A., Jacobsen, F. M., James, S. P., Parry, B. L., Arendt, J., Tamarakin, L. & Wehr, T. A. (1986). Melatonin in seasonal Affective Disorder and phototherapy. *Journal of Neural Transmission*, Suppl. **21**, 257–267.

Sack, R. L. & Lewy, A. J. (1986). Desmethylimipramine treatment increases melatonin production in humans. *Biological Psychiatry* **21**, 406–410.

Sellinger-Barnett, M. M., Mendels, J. & Frazer, A. (1980). The effect of psychoactive drugs on beta-adrenergic receptor binding sites in rat brain. *Neuropharmacology* **19**, 447–454.

Sulser, F. (1979). New perspectives on the mode of action of antidepressant drugs. *Trends in Pharmacological Sciences* **1**, 92–94.

Thompson, C., Mezey, G., Corn, T., Franey, J., English, J., Arendt, J. & Checkley, S. A. (1985). The effect of desipramine upon melatonin and cortisol secretion in depressed and normal subjects. *British Journal of Psychiatry* **147**, 389–393.

Thompson, C., Franey, C., Arendt, J. & Checkley, S. A. (1987). A comparison of melantonin secretion in depressed patients and normal subjects. *British Journal of Psychiatry* (in the press).

Vaughan, G. M., Pelham, R. W., Pang, S. F., Loughlin, L. L., Wilson, K. M., Sandock, K. L., Vaughan, M. K., Koslow, S. H. & Reiter, R. J. (1976). Nocturnal elevation of plasma melatonin and urinary 5-hydroxyindoleacetic acid in young men: attempts at modification by brief changes in environmental lighting and sleep and by autonomic drugs. *Journal of Clinical Endocrinology and Metabolism* **42**, 752–764.

Waldhauser, F., Weissenbacher, G., Zeitlhuber, U., Waldhauser, M., Frisch, H. & Wurtman, R., (1984). Fall in nocturnal serum melatonin levels during prepuberty and pubescence. *Lancet* i, 362–365.

Webley, G. E. & Leidenberger, F. (1986). The circadian pattern of melatonin and its positive relationship with progesterone in women. *Journal of Clinical Endocrinology and Metabolism* **63**, 323–328.

Wehr, T. A., Jacobsen, F. M., Sack, D. A., Arendt, J., Tamarkin, L. & Rosenthal, N. E. (1986). Phototherapy of Seasonal Affective Disorder. *Archives of General Psychiatry* **43**, 870–875.

Wetterberg, L (1983). The relationship between the pineal gland and the pituitary – adrenal axis in health, endocrine and psychiatric conditions *Psychoneuroendocrinology* **8**, 75–80.