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. 1983a). Results from this assay compare well with the reference method of gas chromatography-mass spectrometry (Fraser et al. 1983b).

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 β₁-selective β-adrenoceptor antagonist, atenolol, markedly reduces midnight melatonin levels in normal subjects (Cowen et al. 1983a), suggesting that these receptors are of the β₁-subtype. In patients receiving long-term antihypertensive treatment with β-adrenoceptor antagonists, nocturnal melatonin levels are persistently suppressed (Cowen et al. 1985a).

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

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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 (Claustre 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. 1983b). 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. 1985b; 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. 1985b; 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 \( \beta \)-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.

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REFERENCES


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