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Comparison of the effects of acute fluvoxamine and desipramine administration on melatonin and cortisol production in humans

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1 Acute administration of the specific serotonin uptake inhibitor, fluvoxamine (100 mg at 16.00 h), markedly increased nocturnal plasma melatonin concentrations, with high levels extending into the morning hours.
2 Acute administration of the noradrenaline uptake inhibitor, desipramine (DMI) (100 mg at 16.00 h), increased evening plasma melatonin concentrations.
3 Both drug treatments increased the duration of melatonin secretion, fluvoxamine significantly delaying the offset time and DMI significantly advancing the onset time.
4 The stimulatory effect of DMI on plasma melatonin was mirrored by increased urinary 6-sulphatoxymelatonin (aMT6s) excretion.
5 On the contrary, there was no correlation between plasma melatonin and urinary aMT6s concentrations following fluvoxamine treatment, suggesting that fluvoxamine may inhibit the metabolism of melatonin.
6 Treatment with DMI increased plasma cortisol concentrations in the evening and early morning, treatment with fluvoxamine increased plasma cortisol at 03.00 h, 10.00 h and 11.00 h.
7 The drug treatments affected different aspects of the nocturnal plasma melatonin profile suggesting that the amplitude of the melatonin rhythm may depend upon serotonin availability and/or melatonin metabolism whilst the onset of melatonin production depends upon noradrenaline availability.

Keywords fluvoxamine desipramine melatonin cortisol 6-sulphatoxymelatonin

Introduction

The synthesis and secretion of the pineal gland hormone, melatonin is ultimately dependent upon sympathetic innervation derived from the superior cervical ganglion and terminating in noradrenergic fibres within the pineal gland (for review, Klein [1]). Neural pathways convey signals emanating from the suprachiasmatic nucleus (SCN), via the paraventricular nucleus to the superior cervical ganglion. There is evidence in several species including man, that both α_1 [2], β_1 [3, 4] and α_2-[5–7] adrenergic receptors are involved in the control of melatonin secretion. Data from animal work suggest that the daily rhythm of melatonin secretion is generated in the SCN [8, 9] and is both entrained and suppressed by light [10, 11]. In addition to the importance of these sympathetic neural pathways, the availability of serotonin, the precursor of melatonin, may be a limiting factor in the control of melatonin synthesis [12, 13].

Many reports have shown that pharmacological treatments which increase the availability of biogenic amines, either by inhibition of re-uptake mechanisms [14–17], by inhibition of catabolism by monoamine oxidase [18, 19] or by provision of extra precursor [12, 13] will increase pineal melatonin secretion. However, the relative contributions of the noradrenergic and serotonergic input on the production of melatonin in humans have not been directly evaluated. In order to address this problem, we have assessed the effect of fluvoxamine, a specific serotonin uptake inhibitor, and desipramine (DMI), a noradrenaline uptake inhibitor, on the rhythmic day/night production of plasma melatonin and excretion of the major urinary melatonin metabolite, 6-sulphatoxymelatonin (aMT6s). The effect of these two drugs on the daily plasma cortisol rhythm was also investigated.

Fluvoxamine has previously been reported to increase

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melatonin secretion at night and in the early morning [20, 21]. Studies in our laboratory have shown that DMI, given as a single dose in the late afternoon, will increase melatonin secretion in the early evening [16]. In the present study we have compared the effects of these two antidepressant drugs, given as an acute dose in the early evening, on melatonin and cortisol production in the same individuals.

Methods

Subjects

The study was performed on eight healthy male volunteers aged 21–31 years, with no abnormalities either on medical examination or on screening of haematology or blood biochemistry. All subjects were drug free and within 10% of their ideal body weight. All gave informed consent in writing and approval for the study was granted by the Ethics Committee of the South West Surrey Health Authority.

Treatment

Volunteers on each of three occasions during January and February 1988, received orally either 100 mg fluvoxamine maleate or 100 mg DMI hydrochloride or a matching placebo at 16.00 h. Each treatment was separated by an interval of at least 1 week. The order of drug administration was randomized and the study design was double-blind. For each treatment, subjects remained in a research ward between 15.00 h on the first day and 09.00 h on the second day (lighting < 300 lux). They received a standard meal at 19.30 h and retired to bed at 24.00 h, remaining in darkness (< 1 lux) until 07.00 h.

Plasma samples were taken at hourly intervals for 24 h from 15.00 h on the first day. Blood samples were taken by venepuncture during the first day and an indwelling cannula inserted into a superficial radial vein was used for the night-time and subsequent day sampling. During the night (24.00 h–07.00 h), samples were taken under dim red light (< 1 lux). Commencing at 15.00 h, urine was collected every 3 h for a period of 48 h with the exception of the overnight collections which lasted from 24.00 h until 09.00 h. All samples were stored at −20° C until analysis.

Assays

Samples were assayed for melatonin and cortisol (plasma) and 6-sulphatoxymelatonin (urine). Plasma melatonin levels were measured by direct radioimmunoassay (r.i.a.) as described previously [22]. High baseline values (> 250 pg ml^{-1}) were found in one subject and the direct assay method was thus modified for the measurement of this subject's plasma. A chloroform extraction step was included in the assay procedure and this resulted in normal baseline values of 5 pg ml^{-1}. The minimum detection limit of the assay was 5 pg ml^{-1}. Pools containing 80, 40 and 18 pg ml^{-1} melatonin gave interassay coefficients of variation of 6.9, 11.0 and 22.9%, respectively (n = 48 each). Neither of the antidepressants crossreacted with the melatonin antiserum.

Urine samples were assayed for 6-sulphatoxymelatonin (aMT6s) by direct r.i.a. [23]. The limit of sensitivity of the assay was 0.5 ng ml^{-1}. Interassay coefficients of variation were 10.5, 4.6 and 7.6% (n = 8 each) for mean aMT6s values of 21.3, 5.1 and 2.6 ng ml^{-1}, respectively.

Plasma cortisol concentrations were measured by direct r.i.a. [24]. The minimum detection limit for the assay was 23 nmol l^{-1}. Interassay coefficients of variation were 10.7, 11.8 and 12.0% (n = 18 each) for samples with mean cortisol values of 553, 384 and 88 nmol l^{-1}, respectively.

Statistics

The results are expressed as mean ± s.d. Two-way analysis of variance (ANOVA) was used to determine significant differences between treatments. Where appropriate *post hoc* analysis was performed using the Student-Newman-Keuls' test [25]. The area under the curve (AUC) of the plasma profiles was calculated by the trapezium method [26]. For the purposes of calculation all values below the detection limit of an assay were set at the detection limit.

A plasma melatonin concentration of 15 pg ml^{-1} was significantly greater than the minimum detection limit (+2 s.d.) and was chosen as the reference value to determine the onset and offset times, as well as the duration of an individual's night-time melatonin secretion. Onset and offset clock time values were expressed as decimal values. Acrophases (the estimated time of the peak of the rhythm) were calculated for each individual's plasma melatonin and urinary aMT6s by the method of least-squares using a cosine-curve fitting programme [27].

Results

Plasma melatonin

The mean hourly plasma melatonin concentrations (± s.e. mean) for eight normal subjects following either placebo, 100 mg DMI or 100 mg fluvoxamine are shown in Figure 1. Two-way ANOVA with replication demon-

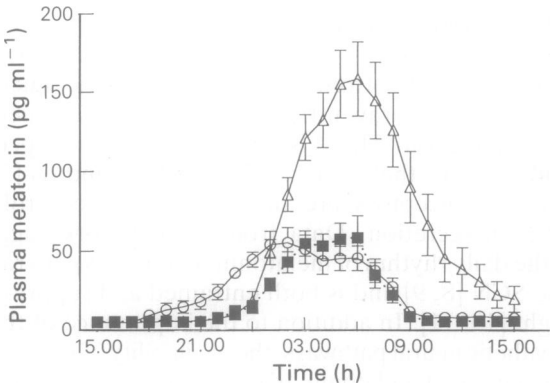

Figure 1 Mean hourly plasma melatonin concentrations (± s.e. mean) in eight healthy male subjects after desipramine (DMI) 100 mg (○), fluvoxamine 100 mg (△) or placebo (■) taken at 16.00 h. Two-way ANOVA indicated significant time-dependent effects of the treatments ($P < 0.001$).

strated: significant differences with the different treatments ($F = 123$, $P \ll 0.001$ d.f. 2, 525); a significant time of day effect ($F = 32$, $P \ll 0.001$ d.f. 24, 525); and a significant interaction between the treatments and the plasma concentrations at different times of day ($F = 8.4$, $P \ll 0.001$ d.f. 48, 525).

Fluvoxamine administration significantly increased overall melatonin secretion (AUC placebo 466 ± 149 pg ml^{-1} h; AUC fluvoxamine 1353 ± 586 pg ml^{-1} h; mean ± s.d., $P < 0.01$) with high plasma concentrations extended into the morning hours (Figure 1). The offset of melatonin secretion was significantly delayed following fluvoxamine treatment (placebo 7.8 ± 1.7 h; fluvoxamine 13.1 ± 3.0 h; $P < 0.01$). This difference in the timing of melatonin secretion was also reflected in the acrophases of the cosine-curves fitted to the plasma melatonin data. Fluvoxamine treatment significantly delayed the acrophase of the plasma melatonin rhythm (placebo 04.00 ± 01.35 h min; fluvoxamine 05.78 ± 1.27 h min; $P < 0.01$). The onset of melatonin secretion after fluvoxamine was not different from the control.

In contrast to fluvoxamine treatment, DMI administration did not significantly increase overall melatonin secretion (AUC placebo 466 ± 149 pg ml^{-1} h; AUC DMI 593 ± 184 pg ml^{-1} h). DMI, however, significantly advanced the time of onset of melatonin secretion by 2–3 h (placebo 23.8 ± 1.4 h; DMI 20.6 ± 1.8 h; $P < 0.01$). This effect produced a significantly earlier acrophase after DMI (02.29 ± 1.69 h min) compared with placebo (04.00 ± 1.35 h min) ($P < 0.01$). The offset of melatonin secretion was unaffected by DMI administration, the offset being similar to placebo treatment.

Both drug treatments significantly increased the duration of melatonin secretion compared with the controls (placebo 8.0 ± 1.6 h; DMI 11.2 ± 2.4 h; fluvoxamine 13.4 ± 3.0 h; $P < 0.01$). The duration of melatonin secretion following fluvoxamine was also significantly longer than after DMI ($P < 0.05$).

These differences in the timing and amplitude of the plasma melatonin profiles were highly reproducible between the individual subjects.

Urinary aMT6s

The total amount of aMT6s excreted during the first 24 h period was significantly higher ($P < 0.01$) following DMI administration (15.25 ± 4.65 μg 24 h^{-1}) compared with control (9.36 ± 2.38 μg 24 h^{-1}) or fluvoxamine (7.55 ± 2.41 μg 24 h^{-1}) treatment. Similarly aMT6s excretion during the second 24 h period was significantly higher ($P < 0.01$) after DMI (15.71 ± 5.09 μg 24 h^{-1}) than following placebo (9.90 ± 2.74 μg 24 h^{-1}) or fluvoxamine (10.37 ± 3.55 μg 24 h^{-1}). During both 24 h periods (day 1 and day 2) there was no statistically significant difference in aMT6s excretion between placebo and fluvoxamine treatment.

The effect of the drug treatments on sequential urinary aMT6s excretion is shown in Figure 2. Urinary aMT6s excretion was significantly increased by DMI treatment compared with placebo or fluvoxamine treatment in the following collection periods: 18.00 h–21.00 h, 21.00 h–24.00 h, 24.00 h–09.00 h and 12.00 h–15.00 h during the first 24 h and 15.00 h–18.00 h, 18.00 h–21.00 h, 21.00 h–24.00 h and 24.00 h–09.00 h during the second

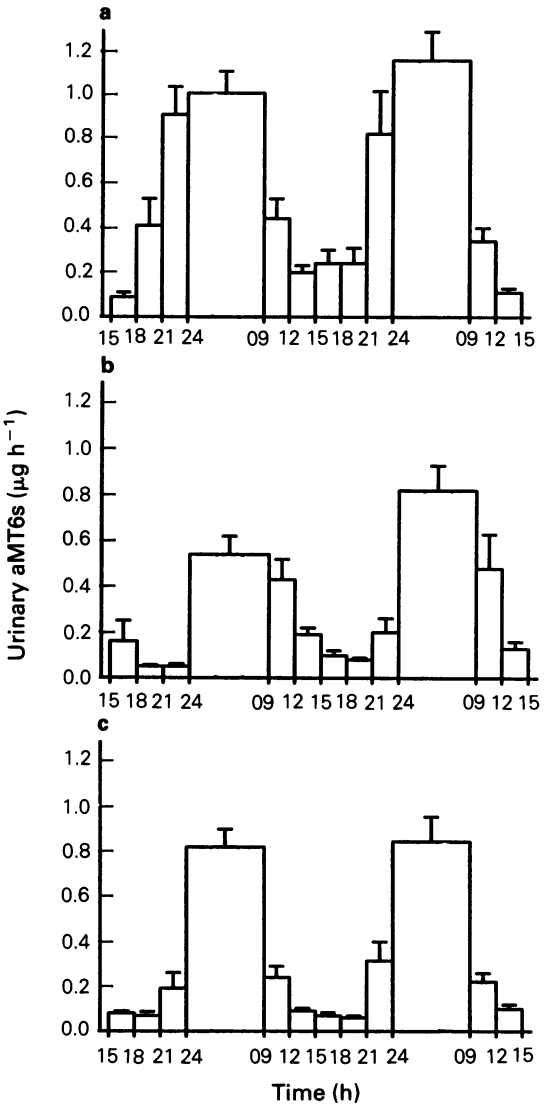

Figure 2 Mean urinary aMT6s excretion (± s.e. mean) after (a) desipramine (DMI) 100 mg, (b) fluvoxamine 100 mg or (c) placebo. Following treatment at 16.00 h on the first day sequential urine collections were made for 48 h. Treatment with DMI significantly increased aMT6s concentrations during the first (18.00 h–09.00 h) and second (15.00 h–09.00 h) 24 h periods ($P < 0.05$–$P < 0.01$). During the first 24 h fluvoxamine treatment reduced aMT6s excretion between 24.00 h–09.00 h ($P < 0.01$) and increased aMT6s excretion between 09.00 h and 15.00 h ($P < 0.05$).

24 h ($P < 0.05$–$P < 0.01$). In contrast, fluvoxamine treatment produced significantly lower aMT6s excretion between 24.00 h–09.00 h during the first 24 h period compared with control or DMI ($P < 0.01$). However, fluvoxamine significantly increased urinary aMT6s concentrations in the subsequent urine collections: 09.00 h–12.00 h and 12.00 h–15.00 h ($P < 0.05$).

The effect of these drugs on the urinary aMT6s excretion rhythm is reflected in the calculated acrophases. The aMT6s acrophase was significantly earlier following DMI (03.88 ± 0.24 h min) and significantly later following fluvoxamine (05.42 ± 0.22 h min) compared with placebo (04.57 ± 0.15 h min) ($P < 0.01$) during the first 24 h of urine collection. In contrast, the aMT6s acrophases were similar for placebo (04.38 ± 0.12 h min),

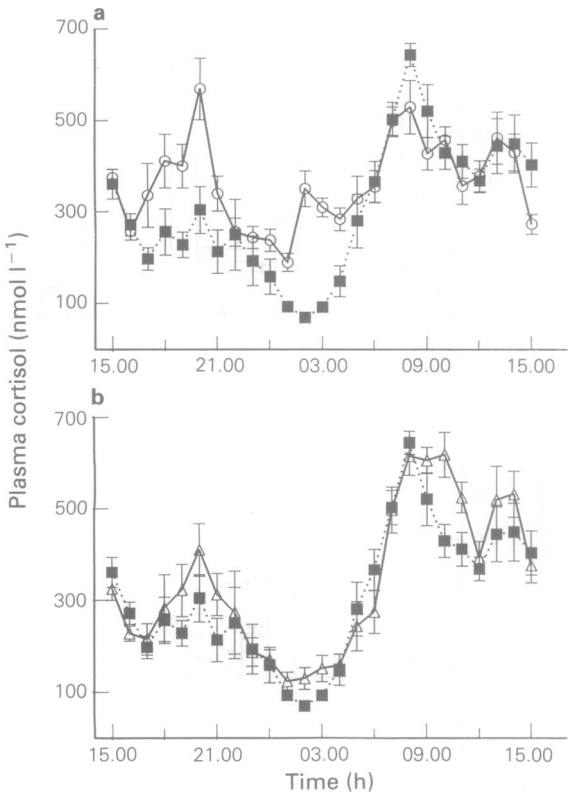

Figure 3 Mean hourly plasma cortisol concentrations (± s.e. mean) after (a) desipramine (DMI) 100 mg (○) or placebo (■) and (b) fluvoxamine 100 mg (△) or placebo (■) taken at 16.00 h. Treatment with DMI significantly increased cortisol levels (18.00 h–20.00 h and 01.00 h–04.00 h, $P < 0.05$–$P < 0.01$). Fluvoxamine increased cortisol concentrations at 03.00 h, 10.00 h and 11.00 h ($P < 0.05$–$P < 0.01$).

DMI (04.03 ± 0.16 h min) and fluvoxamine (04.82 ± 0.22 h min) during the second 24 h collection period.

Plasma cortisol

The mean hourly plasma cortisol concentrations following the different drug treatments are presented in Figure 3. Two-way analysis of variance with replication demonstrated: significant differences with the different treatments ($F = 10$, $P < 0.001$ d.f. 2, 525); a significant time of day effect ($F = 26$, $P < 0.001$ d.f. 24, 525); and a significant interaction between the treatments and the plasma concentrations at different times of day ($F = 2.5$, $P < 0.001$ d.f. 48, 525).

Treatment with DMI significantly increased plasma cortisol concentrations at 18.00 h ($P < 0.05$), 19.00 h, 20.00 h and 01.00 h–04.00 h ($P < 0.01$) compared with placebo. Fluvoxamine administration produced significantly higher cortisol levels at 03.00 h ($P < 0.05$) and 10.00 h–11.00 h ($P < 0.01$) compared with control.

Discussion

Fluvoxamine and DMI administration affected different aspects of the plasma melatonin rhythm. In agreement with our previous study [16], acute administration of DMI at 16.00 h significantly advanced the onset of melatonin secretion but did not affect the amplitude or offset of melatonin secretion. These results suggest that the timing of the evening onset of melatonin secretion is dependent upon noradrenergic mechanisms. Animal work has shown a marked daily variation in the number of pineal β-adrenoceptors with maximum receptor sensitivity at the end of daylight [28]. Treatment with DMI in the late afternoon thus increased noradrenaline availability (by inhibiting its re-uptake) at a time of maximum receptor sensitivity. Both conditions appear to be necessary for stimulation of melatonin secretion as morning administration of DMI failed to affect plasma melatonin concentration [16].

These observations are also supported by our previous findings that (+)-oxaprotiline, a potent and selective inhibitor of noradrenaline uptake, given at 21.00 h increased plasma melatonin concentrations whereas (−)-oxaprotiline, an inactive noradrenaline uptake inhibitor, had no effect on melatonin concentrations [14, 17]. Given at 09.00 h neither of these drugs affected melatonin secretion [14].

The stimulatory effect of DMI on melatonin secretion was also reflected in the urinary excretion of the melatonin metabolite, aMT6s. Significantly enhanced aMT6s excretion occurred on both days between 18.00 h and 09.00 h following DMI administration. These results show that the evening increase in plasma melatonin was not due to DMI inhibition of melatonin metabolism which confirms the findings of our previous study [16].

Fluvoxamine treatment on the other hand, markedly increased the amplitude of the nocturnal plasma melatonin profile and significantly delayed the offset of melatonin secretion in all of the subjects. Our results agree with a previous finding showing enhanced night-time plasma melatonin concentrations and a delayed offset following fluvoxamine treatment [20, 21].

The stimulatory effect of fluvoxamine on plasma melatonin concentrations in our study, however, was not reflected in the amount of urinary aMT6s excreted. On the contrary, fluvoxamine treatment produced significantly lower aMT6s excretion between 24.00 h–09.00 h during the first 24 h compared with control. Even though increased aMT6s concentrations were observed in the subsequent urine collections 09.00 h–12.00 h and 12.00 h–15.00 h following fluvoxamine, these levels were not of sufficient magnitude to increase the overall 24 h aMT6s excretion. In both the first and second 24 h periods excretion of aMT6s following fluvoxamine was similar to placebo.

It could be argued that the different effects of desipramine and fluvoxamine on melatonin production reflect different pharmacokinetic profiles of the drugs. Although plasma levels of desipramine and fluvoxamine were not measured in this study, previous pharmacokinetic studies do not support this idea. Administration of DMI (100 mg orally at 16.00 h) produced maximum plasma DMI concentrations of 24 ng l^{-1} 3 h after administration which remained above 20 ng l^{-1} for 17 h [16]. Following a single 100 mg dose of fluvoxamine peak plasma concentrations of 31–87 μg l^{-1} were reached 2–8 h after administration [29]. Based on these studies it is assumed that adequate plasma concentrations were achieved prior to the onset of the night-time melatonin secretion.

Which pharmacological property of fluvoxamine caused the elevated plasma melatonin levels is not clear. A number of possible actions have been proposed: a serotonin-noradrenergic mechanism affecting β-adrenoceptor sensitivity; intracellular serotonin availability; increased density of platelet α_2-adrenoceptors [21]. Of these serotonin availability would be the most likely mechanism underlying the acute effect of fluvoxamine. In previous studies of healthy untreated subjects, urinary aMT6s concentrations have proved to be a reliable reflection, both qualitative and quantitative, of plasma melatonin levels [4, 30]. However, in view of our findings of a lack of correlation between plasma melatonin and urinary aMT6s concentrations following fluvoxamine treatment, the possibility that fluvoxamine inhibits the hepatic metabolism of melatonin and therefore delays its clearance from the plasma must be considered. The relative contributions of the inhibition of melatonin metabolism and increased serotonin availability on plasma melatonin concentrations, however, are impossible to assess in this study. Whether the elevated plasma melatonin levels following fluvoxamine administration were entirely due to inhibition of melatonin metabolism requires further investigation.

In man melatonin is metabolised in the liver into 6-hydroxymelatonin followed by sulphate (59–65%) or glucuronide (24–27%) conjugation [31]. Exogenously administered melatonin has a short half life (20–60 min) with a high hepatic first pass effect [32, 33]. The major metabolites of fluvoxamine (65%) are produced by oxidative demethylation of the aliphatic methoxyl group of the parent compound [34]. Fluvoxamine co-administration has been reported to markedly increase the plasma concentrations of warfarin and propranolol [35]. The mechanism of these drug interactions as well as the proposed interaction between fluvoxamine and melatonin requires further study.

The effect of the drug treatments on the plasma cortisol rhythm was less clear cut than on the plasma melatonin rhythm. Administration of DMI significantly increased plasma cortisol in the evening 18.00 h–20.00 h and in the early morning 01.00 h–04.00 h. Fluvoxamine treatment significantly increased plasma cortisol at 03.00 h, 10.00 h and 11.00 h. Plasma cortisol concentrations increased 1–2 h earlier (02.00–03.00 h) following fluvoxamine compared with placebo. These latter results agree with the study of Demisch *et al.* [20] who found that fluvoxamine (150 mg at 19.00 h) increased plasma cortisol levels earlier (at 04.00 h) compared with the control sampling period the night before. These effects on the cortisol rhythm may be secondary to the effects on melatonin or due to a direct effect on the SCN-generated rhythm.

In conclusion, fluvoxamine and DMI did not affect the nocturnal plasma melatonin rhythm in the same way which suggests differential effects of noradrenergic and serotonergic mechanisms on melatonin production. The amplitude of the melatonin rhythm may be dependent upon serotonin availability and/or melatonin metabolism whereas the onset (but not offset) of melatonin production appears to be dependent upon noradrenaline availability.

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