

## Abnormality of Circadian Rhythm of Serum Melatonin and Other Biochemical Parameters in Fibromyalgia Syndrome

Abbas Ali Mahdi<sup>1\*</sup>, Ghizal Fatima<sup>1</sup>, Siddhartha Kumar Das<sup>2</sup> and Nar Singh Verma<sup>3</sup>

<sup>1</sup>Departments of Biochemistry, <sup>2</sup>Rheumatology and <sup>3</sup>Physiology, C.S.M. Medical University U.P, Lucknow, 226 003, India

*Received 13 October 2010; revised 27 February 2011*

Fibromyalgia syndrome (FMS) is a complex chronic condition causing widespread pain and variety of other symptoms. It produces pain in the soft tissues located around joints throughout the body. FMS has unknown etiology and its pathophysiology is not fully understood. However, abnormality in circadian rhythm of hormonal profiles and cytokines has been observed in this disorder. Moreover, there are reports of deficiency of serotonin, melatonin, cortisol and cytokines in FMS patients, which are fully regulated by circadian rhythm. Melatonin, the primary hormone of the pineal gland regulates the body's circadian rhythm and normally its levels begin to rise in the mid-to-late evening, remain high for most of the night, and then decrease in the early morning. FMS patients have lower melatonin secretion during the hours of darkness than the healthy subjects. This may contribute to impaired sleep at night, fatigue during the day and changed pain perception. Studies have shown blunting of normal diurnal cortisol rhythm, with elevated evening serum cortisol level in patients with FMS. Thus, due to perturbed level of cortisol secretion several symptoms of FMS may occur. Moreover, disturbed cytokine levels have also been reported in FMS patients. Therefore, circadian rhythm can be an important factor in the pathophysiology, diagnosis and treatment of FMS. This article explores the circadian pattern of abnormalities in FMS patients, as this may help in better understanding the role of variation in symptoms of FMS and its possible relationship with circadian variations of melatonin, cortisol, cytokines and serotonin levels.

**Keywords:** Fibromyalgia syndrome, Circadian rhythm, Melatonin, Cortisol, Serotonin, IL-6, TNF-alpha

### Introduction

Fibromyalgia syndrome (FMS) is characterized by pronounced fatigue and widespread musculoskeletal pain, which occurs for more than 3 months along with the presence of 11 out of 18 tender points<sup>1</sup>. FMS is usually considered a disorder of women between 20 to 50 yrs of age; however, it has also been observed in males, children, adolescents, and older persons. The prevalence of FMS based on the 1990 ACR (American College of Rheumatology) classification criteria in the general population of the USA is reported to be 3.4% in women and 0.5% in men<sup>2</sup>. In a study from Brazil, FM was found to be present in

4.4% of the population. Its prevalence increases steadily upto 80 yrs of age, and then declines and it affects women 10-times more often than men<sup>3</sup>.

FMS patients have a number of symptoms which include disturbed sleep, emotional distress, irritable bowel syndrome, chronic fatigue syndrome, restless leg syndrome, major depression, irritable bladder, dysmenorrhoea and neuropathic pain<sup>4</sup>. However, current evidence indicates that FMS is a hyperalgesic state, resulting from generalized problem of augmented pain processing. It has been reported that in FM patients the descending pain pathway involving serotonin, norepinephrine and dopamine, as opposed to the descending opioid pain pathway, is selectively attenuated<sup>5</sup>. Moreover, FM is also considered to be a disorder of central pain processing that produces heightened responses to painful stimuli (hyperalgesia) and painful responses to non-painful stimuli (allodynia). Therefore, the heightened state of pain transmission may be due to increase in pronociceptive neurotransmitters, such as substance P and glutamate<sup>6</sup>. Thus, the pain of FMS is often accompanied by one or

\* Author for correspondence

Tel.: 0091-522-2257576

Fax: 0091-522-2253030

E-mail: mahdiaa@rediffmail.com

*Abbreviations:* ACTH, adeno-cortico-tropic hormone; CNS, central nervous system; CSF, cerebrospinal fluid; FM, fibromyalgia; FMS, fibromyalgia syndrome; HPA, hypothalamic-pituitary-adrenal; IL-6, interleukin-6; SCN, suprachiasmatic nucleus.

more manifestations, such as affective moods, cognitive insecurity, autonomic dysfunction, or irritable bowel syndrome. However, the new findings from brain imaging and polysomnography imply that FMS may be a disorder of premature neurologic aging<sup>7</sup>.

There have been reports that the changes in the neuronal activity of CNS, abnormal metabolism of biogenic amines, and immunological disorders may contribute to the development of FMS<sup>8</sup>. In the pathophysiology of FMS, the biologic, genetic, and environmental factors may also be responsible. There is strong evidence that cardinal pain symptoms of FMS may occur due to alterations in central processing of sensory input, along with aberrations in the endogenous inhibition of pain<sup>9</sup>. Some studies suggest that FMS may occur as a result of low serotonin states<sup>10</sup>, sleep disorders and<sup>11</sup>, endocrine disorders. However, the exact cause of FMS is not known. This article reviews the abnormal circadian rhythm in symptoms of FMS and the alternations in the pattern of release of melatonin, serotonin, cortisol and cytokines (Fig. 1).

**Circadian rhythm in FMS**

The circadian system is organized in a hierarchical manner and a central pacemaker in the suprachiasmatic nucleus (SCN) of the hypothalamus synchronizes cellular circadian oscillators in most peripheral body cells. SCN is responsible for controlling circadian rhythms and generates many neuronal and hormonal signals which regulate body functions in a 24-h cycle. Fasting-feeding cycles accompanying rest-activity rhythms are the major timing cues in the synchronization of circadian clock,

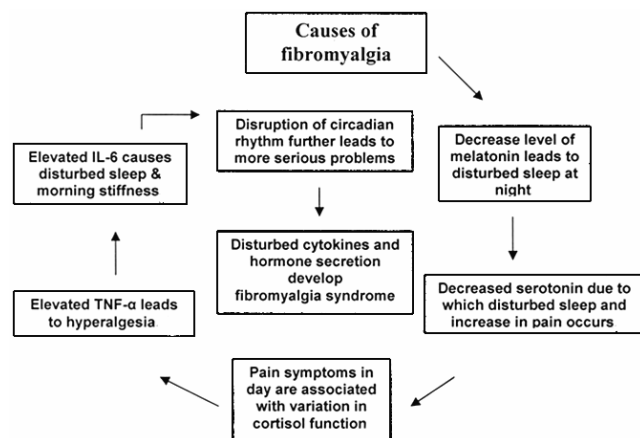


Fig. 1—Disturbed level of cytokines and hormonal profiles are responsible for the causes of fibromyalgia syndrome

suggesting that the temporal coordination of metabolism is a major task of the human timing system (Fig. 2). Many aspects of human behavior and physiology show circadian rhythmicity, including sleep, physical activity, alertness, hormone levels, body temperature, immune functions and digestive activity. Remarkably, all of these diverse rhythms are controlled by SCN, and rhythms are lost, if the SCN is destroyed. For example, in case of sleep in rats the total amount is maintained even with SCN damage, but the length and timing of sleep become erratic.

Light cues the body to produce cortisol, serotonin, melatonin and other hormones and neurotransmitters which are responsible for controlling the normal circadian rhythm of various profiles including sleep/wake cycle, blood pressure, and body temperature. However, the normal rhythm of secretion of these hormones gets disturbed in patients with FMS. Therefore, many of the symptoms associated with FMS (difficulty in sleeping, fatigue, malaise, myalgias, gastrointestinal complaints and decreased cognitive function) are similar to those observed in individuals whose circadian pacemaker is abnormally aligned with their sleep-wake schedule and/or with local environmental time. Sleep disturbances have been recognized as one of the most probable cause of FMS<sup>12</sup>. The increase of cyclic alternating pattern rate indicates a worst quality of sleep in patients with FMS. This is strongly correlated to the severity of FMS symptoms<sup>13</sup>.

**Melatonin**

Melatonin is produced at night from 5-hydroxy tryptophan (5-HT), and it displays dynamic circadian rhythms in both synthesis and release<sup>14</sup>. Because of the close association of pineal melatonin release with

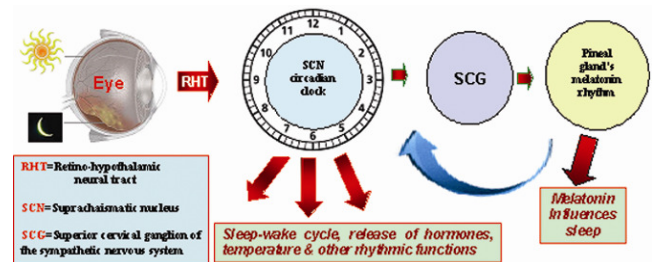


Fig. 2—Influence of light and dark on circadian rhythm and related physiology and behavior through the SCN (the circadian clock of the brain) in humans [The SCN generates circadian rhythms which are synchronized to 24 h mostly by light. Melatonin influences the timing and overall activity of the SCN and may also affect the function of the retina]

the clock activity, melatonin has been regarded as an accurate marker of the circadian pacemaker for both animal and human circadian rhythm studies<sup>15,16</sup>. Melatonin is the mediator of external light to physiologic adaptation during day and night rhythms and facilitates sleep levels, which are highest during night and decreases during the day<sup>17</sup>. However, other studies comparing melatonin levels in patients with FMS to healthy controls have shown variable results ranging from normal<sup>18</sup>, decreased<sup>19</sup> to increased<sup>20</sup> melatonin levels. These results indicate that both 5-HT and melatonin could serve as reliable markers of the circadian clock because of their day-to-day precision of onset timings<sup>21</sup>.

### Cortisol

Cortisol which is a marker of stress follows a circadian rhythm with its elevated level in the morning and decreased levels during night. However, the altered functioning of the Hypothalamic-pituitary-adrenal axis (HPA) is reported to be an important factor in the perturbation of circadian symptoms of FMS. Studies have shown blunting of the normal diurnal cortisol rhythm, with elevated evening serum cortisol levels in FMS patients<sup>22,23</sup>. But, most of the studies have revealed low 24-h urinary free cortisol excretion, exaggerated ACTH release in response to corticotropin-releasing challenge and abnormal diurnal rhythmicity in the secretion of cortisol<sup>24</sup>. The pattern of differences for basal circadian architecture of HPA axis hormones differs between patients with FMS and chronic fatigue syndrome (CFS) compared to their matched control groups. The abnormalities in FMS patients are consistent with loss of HPA axis<sup>25</sup>; however, depression in FMS patients is due to the disturbances in the HPA axis<sup>26</sup>.

### Serotonin

Serotonin or 5-hydroxytryptamine (5-HTP) is a monoamine neurotransmitter which is implicated in psychiatric disorders, such as depression and anxiety. However, interest has been growing in the possible involvement of 5-HT in FM. Indeed, strong evidence has accumulated to support the hypothesis that deficiency in serotonergic neuronal functioning might be related to the pathophysiology of FM<sup>27</sup>. In one of the studies, lower levels of serotonin breakdown metabolites have been found in the CSF of a group of FMS patients, as well as in patients with rheumatoid arthritis<sup>28</sup>. In neurochemical pathogenesis of FMS<sup>29</sup>

and in other studies, both low levels of tryptophan<sup>30</sup> and serotonin<sup>31</sup> in the serum and low levels of tryptophan and 5-HTP in the CSF have been found in FMS patients<sup>32</sup>. Low serum serotonin levels in patients with FMS have been found to have an inverse correlation with clinical measures of perceived pain<sup>33</sup>.

### Cytokines

Consistently, human cytokine production exhibits a diurnal rhythmicity with peak levels during the night and in early morning, at a time when plasma cortisol is lowest and melatonin is highest. The 24-h secretory pattern of IL-6 in healthy young adults suggests that IL-6 is secreted in a biphasic circadian pattern with two nadirs at about 08.00 and 21.00, and two zeniths at about 19.00 and 05.00 h. Thus, IL-6 is a mediator of sleepiness and its circadian pattern reflects the homeostatic drive for sleep<sup>34</sup>. Women with FMS have shown a delayed rise in adeno-cortico-tropic hormone (ACTH) in response to interleukin-6 (IL-6) administration<sup>35</sup>. Evidence from a psychoneuroimmunological study in patients with FMS suggests a disturbed HPA axis function, which requires enhanced IL-6 levels<sup>36</sup>. However, in a study on circadian rhythm, no significant difference has been found in between the women with FM and control in the circadian amplitude or phase of rhythms of melatonin, cortisol and core body temperature. Both groups of women have shown similar circadian rhythms in self-reported alertness, although pain and stiffness are significantly increased in women with FM compared with healthy women<sup>37</sup>.

### Circadian variation of symptoms in FMS

Epidemiologic studies show that non-restorative sleep is an important component of FMS, which is caused by the disturbed level of melatonin in the hour of darkness. Due to perturbed melatonin level, night time sleep is disturbed in patients with FMS causing pain in the early morning. The daytime symptoms, in patients with FMS like headache, stiffness, fatigue and pain are not fixed throughout the day. However, stiffness and musculoskeletal pain are more prominent in early morning. An examination of circadian sleep-wake-related functions shows that the symptoms of FMS vary over the course of the day. However, normal subjects have their lowest sensitivity of pain in the morning, patients with FMS have increased tenderness in the morning, or no overnight improvement in pain due to disturbed sleep at night<sup>38</sup> (Fig. 3).

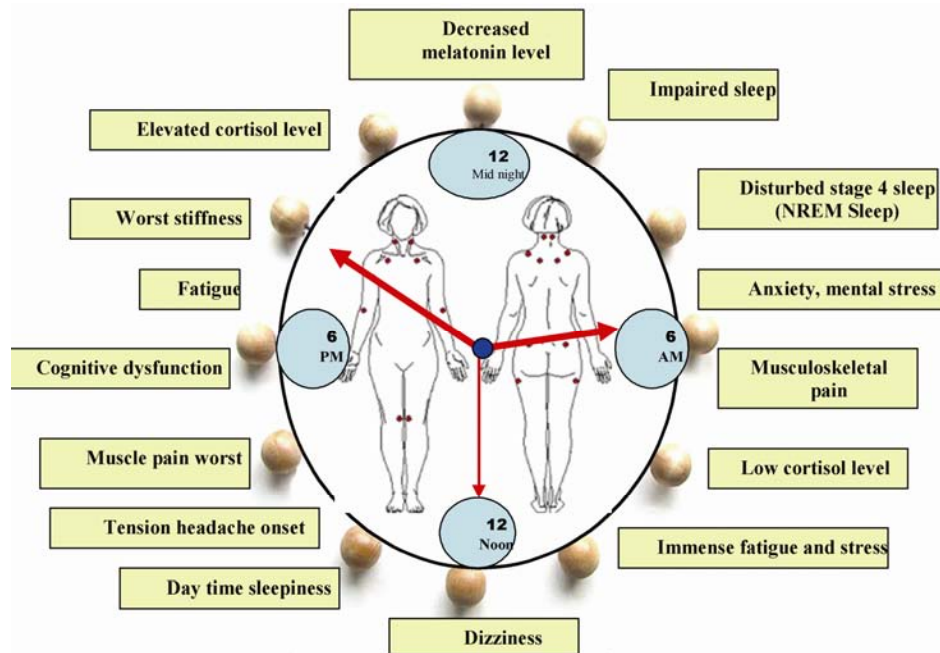


Fig. 3—FMS [Circadian rhythm of symptoms]

In women with FMS, pain symptoms early in the day are associated with variations in function of the HPA axis<sup>39</sup>. The primary FMS shows a circadian rhythm of the symptoms and severe pain in winter season. Although the pathophysiologic mechanisms are unknown, the circadian variations are well documented in the literature and the seasonality of pain is clinically reported<sup>40</sup>. Patients with FM have diurnal impairment in speed of performance of complex cognitive tasks, which accompany light stage 1 electroencephalographic (EEG) sleep and their experience of pain and non-restorative sleep symptoms of sleepiness, fatigue, and negative mood<sup>41</sup>.

The pain and fatigue tend to decline, from mid morning to mid afternoon, and after 3 p.m. patients commonly complain that they have hit “a brick wall” with fatigue and are unable to think properly or carry out any meaningful tasks<sup>42</sup>.

When the patients with FMS go to bed at night, they feel no better than when they awaken the following morning. Overall, the disturbances in sleep physiology contribute to the poor quality of sleep and the vicious cycle of unrefreshing sleep, morning aching, stiffness, and fatigue<sup>42,43</sup>. It has also been postulated that a change in melatonin secretion causes changes in sleep, pain, somatotrophic axis and HPA axis<sup>44</sup>. Thus, due to this blunting in level of cortisol, melatonin, serotonin and cytokines, several symptoms of FMS may occur causing circadian rhythm

disturbances in these patients which may contribute to impaired sleep at night, fatigue during the day, and causes changed pain perception.

The pro-inflammatory cytokines are often elevated in FM patients, suppressing the circadian output signals, resulting in the symptoms of FMS such as fatigue, appetite loss and sleep disruption. Since the serum level of pro-inflammatory cytokines follows the circadian rhythm in healthy individuals, it is likely that the synthesis and secretion of pro-inflammatory cytokines are controlled or modulated by the circadian clock<sup>45</sup>. Disruption of the circadian rhythm could lead to deregulation of pro-inflammatory cytokine. It could also disrupt the circadian rhythm in behavior and physiology at the organism level<sup>46</sup>. Thus, shift in cytokines production may play a crucial role in generating symptoms of FM, but its relationship to circadian rhythm of symptoms is not known.

### Is Circadian rhythm important in diagnosis and treatment of FMS?

Circadian rhythms control the timing, quantity and quality of the hormones and neurotransmitters that the body produces and eventually secretes. Hormones and neurotransmitters are the elements that determine how we feel, our sleep patterns, our appetite, our sex drive and other sleep and mood-related issues. And, when functioning properly, our circadian rhythms create circadian balance. When out of balance, quantity,

quality and timing of hormone and neurotransmitter secretion is hampered and there is a disturbed circadian rhythm.

In disturbed circadian rhythm state, body produces hormones, chemicals and neurotransmitters in perturbed amounts and/or at the wrong time of the day. Also in FMS melatonin is produced less at bed time which affects sleep. One non-placebo controlled study has shown a beneficial effect of melatonin supplementation on FMS<sup>47</sup>. Another recent study reports that the administration of melatonin is effective in treating pain associated with FMS<sup>48</sup>. Rating of pain, stiffness, and fatigue in FM are significantly correlated and show diurnal and possibly weekly rhythmicity, especially when pain threshold is low. This has important implications for scheduling activities of daily living for measurement in clinical trials and possibly for timing the administration of medications<sup>49</sup>.

Circadian rhythms stimulate the timing and production of many hormones and chemicals that affect sleep and mood. If we know that at what time of the day which symptoms of FMS occur then it would be helpful in designing the treatment line. The mammalian circadian system is organized in a hierarchical manner in a central pacemaker (SCN) of the brain's hypothalamus which synchronizes cellular circadian oscillators in most peripheral body cells. Fasting-feeding cycles accompanying rest-activity rhythms are the major timing cues in the synchronization of many peripheral clocks, suggesting that the temporal coordination of metabolism and proliferation is a major task of the mammalian timing system. The rhythmic control of xenobiotic detoxification provides the molecular basis for scheduling the dose at a specific time, so as to improve its efficacy and also to reduce its toxicity. Therefore, the circadian rhythm can be used in improving chronotherapeutics for the FMS patients<sup>50</sup>.

### Conclusion

In recent years, FMS has become a serious social problem in the well developed countries. Therefore, efforts are to be made to properly diagnose FM and to devise its appropriate treatment modalities. As discussed here, it seems that circadian rhythmicity can be important in the pathophysiology, diagnosis and treatment of FMS. Therefore, it may be stated that the changes in serotonin, melatonin, cortisol and cytokines (IL-6 and TNF-alpha) levels raise the

possibility that there is an abnormality of circadian rhythm of these parameters in FMS patients. However, to the best of our knowledge no controlled studies of circadian rhythm have been performed in patients with FMS. Therefore, a clear understanding on circadian pattern of FMS symptoms will provide useful information to augment the understanding of its pathophysiology and help in the proper diagnosis and treatment of FMS.

### References

- 1 Wolfe F, Smythe H A, Yunus M B, Bennett R M, Bombardier C, Goldenberg D L, Tugwell P, Campbell S M, Abeles M, Clark P, Fam A G, Farber S J, Fiechtner J J, Franklin C M., Gatter R A, Hamaty D, Lessard J, Lichtbroun A S & Masi A T (1990) The American College of Rheumatology criteria for the classification of fibromyalgia. *Arthritis Rheum* 33, 160-172
- 2 Wolfe F, Ross K, Anderson J, Russell I J & Hebert L (1995) The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 38, 19-28
- 3 Assumpção A, Cavalcante A B, Capela C E, Sauer J F, Chalot S D, Pereira C A & Marques A P (2009) Prevalence of fibromyalgia in a low socioeconomic status population. *BMC Musculoskelet Disord*, 10:64-71
- 4 Maletic V & Raison C L (2009). Neurobiology of depression, fibromyalgia and neuropathic pain. *Front Biosci* 14, 5291-5338
- 5 Arnold L M (2010) The Pathophysiology, Diagnosis and Treatment of Fibromyalgia. *Psychiatr Clin North Am* 33, 375-408
- 6 Clauw D J (2009) Fibromyalgia: An Overview. *Am J Med* 122, S3-S13
- 7 Russell I J & Larson A A (2009) Neurophysiopathogenesis of Fibromyalgia Syndrome: A Unified Hypothesis. *Rheum Dis Clin North Am* 35, 421-435
- 8 Podolecki T, Podolecki A & Hrycek A (2009) Fibromyalgia: pathogenetic, diagnostic and therapeutic concerns. *Pol Arch Med Wewn* 119, 157-161
- 9 Bradley L A (2009) Pathophysiology of Fibromyalgia. *Am J Med* 122, S22-S30
- 10 Harding S (1998) Sleep in Fibromyalgia Patients: Subjective and Objective Findings. *Am J Med Sci* 315, 367-376
- 11 Gur A, Karakoç M, Nas K, Çevik R, Saraç A J & Demir E (2002) Cytokines IL-6 & IL-8 is found to be elevated in patients with FMS. *J Rheumatol* 29, 358-361
- 12 Schaefer K M (2003) Sleep disturbances linked to fibromyalgia. *Holist Nurs Pract* 17, 120-127
- 13 Rizzi M, Sarzi-Puttini P & Atzeni F (2004) Cyclic alternating pattern: a new marker of sleep alteration in patients with fibromyalgia. *J Rheumatol* 31, 1193-1199
- 14 Sun X, Deng J, Liu T & Borjigin J (2002) Circadian 5-HT production regulated by adrenergic signaling. *Proc Natl Acad Sci (USA)* 99, 4686-4691
- 15 Arendt J (2006) Melatonin and human rhythms. *Chronobiol Int* 23, 21-37
- 16 Lewy A J, Cutler N L & Sack R L (1999) The endogenous melatonin profile as a marker for circadian phase position. *J Biol Rhythms* 14, 227-236



- 17 Wikner J, Hirsch U, Wetterberg L & Rodjmark S (1998) Fibromyalgia: a syndrome associated with decreased nocturnal melatonin secretion. *Clin Endocrinol* 49, 179-183
- 18 Press J, Phillip M & Neumann L (1998) Normal melatonin levels in patients with fibromyalgia syndrome. *J Rheumatol* 25, 551-555
- 19 Wikner J, Hirsch U, Wetterberg L & Rodjmark S (1998) Fibromyalgia: a syndrome associated with decreased nocturnal melatonin secretion. *Clin Endocrinol* 49, 179-183
- 20 Korszun A, Sackett-Lundeen L & Papadopoulos E (1999) Melatonin levels in women with fibromyalgia and chronic fatigue syndrome. *J Rheumatol* 26, 2675-2680
- 21 Liu T & Borjigin J (2006) Relationship between nocturnal serotonin surge and melatonin onset in rodent pineal gland. *J Circadian Rhythms*, 10, 4-12
- 22 Crofford L J, Pillemer S R & Kalogeras K T (1994) Hypothalamic-pituitary-adrenal axis perturbations in patients with fibromyalgia. *Arthritis Rheum* 37, 1583-1592
- 23 McCain G A & Tilbe K S (1989) Diurnal hormone variation in fibromyalgia syndrome: a comparison with rheumatoid arthritis. *J Rheumatol* 16, 154-157
- 24 Adler G K, Kinsley B T, Hurwitz S, Mossey C J & Goldenberg D L (1999) Reduced Hypothalamic-pituitary and sympathoadrenal responses to hypoglycemia in women with fibromyalgia syndrome. *Am J Med* 106, 534-543
- 25 Crofford L J, Young E A & Engleberg N C (2004). Basal circadian and pulsatile ACTH and cortisol secretion in patients with fibromyalgia and/or chronic fatigue syndrome. *Brain Behav Immun* 18, 314-325
- 26 Wingenfeld K, Nutzinger D, Kauth J, Hellhammer D H & Lautenbacher S (2010) Salivary cortisol release and hypothalamic pituitary adrenal axis feedback sensitivity in fibromyalgia is associated with depression but not with pain. *J Pain* 11, 1195-1202
- 27 Neeck G (2002) Pathogenic mechanisms of fibromyalgia. *Ageing Res Rev* 2, 243-255
- 28 Russell I J, Vaeroy H, Javors M & Nyberg F (1992) Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. *Arthritis Rheum* 35, 550-556
- 29 Russell I J (1998) The neurochemical pathogenesis of fibromyalgia syndrome. *J Rheumatol* 57 (Suppl), 63-66
- 30 Yunus M B, Dailey J W & Aldag J C (1992) Plasma tryptophan and other amino acids in primary fibromyalgia: a controlled study. *J Rheumatol* 19, 90-94
- 31 Hrycaj P, Stratz T & Muller W (1993) Platelet 3H-imipramine uptake receptor density and serum serotonin levels in patients with fibromyalgia/ fibrositis syndrome. *J Rheumatol* 20, 86-88
- 32 Russell I J, Vipraio G A & Acworth I (1993) Abnormalities in the central nervous system metabolism of tryptophan to 3-hydroxy kynurenine in fibromyalgia syndrome. *Arthritis Rheum* 36, S222
- 33 Russell I J, Michalek J E & Vipraio G A (1992) Platelet 3H-imipramine uptake receptor density and serum serotonin levels in patients with fibromyalgia/fibrositis syndrome. *J Rheumatol* 19, 104-109
- 34 Vgontzas A N, Bixler E O, Lin H M, Prolo P, Trakada G & Chrousos G (2005) IL-6 and Its Circadian Secretion in Humans. *Neuroimmunomodulation* 12, 131-140
- 35 Torpy D J, Papanicolaou D A, Lotsikas A J, Wilder R L, Chrousos G P & Pillemer S R. (2000) Responses of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis to interleukin-6: a pilot study in fibromyalgia. *Arthritis Rheum* 43, 872-880
- 36 Geiss A, Rohleder N & Anton F (2006) Does a disturbed HPA axis function require enhanced IL-6 levels? Evidence from a psychoneuroimmunological study in fibromyalgia patients. *Brain Behavior Immunity* 20, 23-24
- 37 Klerman E B, Goldenberg D L, Brown E N, Maliszewski A M, and Adler G K (2001) Circadian Rhythms of Women with Fibromyalgia. *J Clin Endocrinol & Metab* 86, 1034-1039
- 38 McLean S A, Williams D A, Harris R E, Kop W J, Groner K H & Ambrose K (2006) Momentary relationship between cortisol secretion and symptoms in patients with fibromyalgia. *Arthritis Rheum* 54, 2345-2346
- 39 Pöhlmann L (1994) Fibromyalgia: chronobiological aspects. *Chronobiol Int* 11, 393-396
- 40 Czeisler C A, Dijk D J, Takahashi J S, Turek F W & Moore RY (2001) Human circadian physiology and sleep-wake regulation. In: *Handbook of behavioral neurobiology: circadian clocks*, pp 531-569, Plenum Press, New York
- 41 Moldofsky H (1995) Sleep, neuroimmune and neuroendocrine functions in fibromyalgia and chronic fatigue syndrome. *Adv Neuroimmunol* 5, 39-56
- 42 Roizenblatt S, Moldofsky H, Bedito-Silva A A & Tufik S (2001) Alpha sleep characteristics in fibromyalgia. *Arthritis Rheum* 44, 222-230
- 43 Crofford L J, Pillemer S R & Kalogeras K T (1994) Hypothalamic-pituitary-adrenal axis perturbations in patients with fibromyalgia. *Arthritis Rheum* 37, 1583-1592
- 44 Webb S M (1998) Fibromyalgia and melatonin: are they related? *Clin Endocrinol* 49, 161-162
- 45 Loning Fu (2007) Understanding the Mechanism of Circadian Modulation to Improve the Quality of Life for Cancer Patients. *J Support Oncol* 5, 176-177
- 46 Petrovsky N & Harrison L C (1998) The chronobiology of human cytokine production. *Int Rev Immunol* 16, 635-649
- 47 Citera G, Arias M A & Maldonado J A (2000) The effect of melatonin in patients with fibromyalgia: a pilot study. *Clin Rheumatol* 19, 9-13
- 48 Hussain S A, Al-Khalifa I I, Jasim N A & Gorial F I (2010) Adjuvant use of melatonin for treatment of fibromyalgia. *J Pineal Res* doi: 10.1111/j.1600-079X.2010.00836.x
- 49 Bellamy N, Sothorn R B & Campbell J (2004) Aspects of diurnal rhythmicity in pain, stiffness, and fatigue in patients with fibromyalgia. *J Rheumatol* 31, 379-89
- 50 Levi F & Schibler U (2007) Circadian rhythms: mechanisms and therapeutic implications. *Annu Rev Pharmacol Toxicol* 47, 593-628