

Review

Association Between Mobile Phone Radiation Exposure and the Secretion of Melatonin and Cortisol, Two Markers of the Circadian System: A Review

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The extremely important use of mobile phones in the world, at all ages of life, including children and adolescents, leads to significant exposure of these populations to electromagnetic waves of radiofrequency. The question, therefore, arises as to whether exposure to these radiofrequencies (RFs) could lead to deleterious effects on the body's biological systems and health. In the current article, we review the effects, in laboratory animals and humans, of exposure to RF on two hormones considered as endocrine markers: melatonin, a neurohormone produced by the pineal gland and cortisol, a glucocorticosteroid synthesized by the adrenal glands. These two hormones are also considered as markers of the circadian system. The literature search was performed using PubMed, Medline, Web of Sciences (ISI Web of Knowledge), Google Scholar, and EMF Portal. From this review on RF effects on cortisol and melatonin, it appears that scientific papers in the literature are conflicting, showing effects, no effects, or inconclusive data. This implies the need for additional research on higher numbers of subjects and with protocols perfectly controlled with follow-up studies to better determine whether the chronic effect of RF on the biological functioning and health of users exists (or not). Bioelectromagnetics. 2021;42:5–17. © 2020 Bioelectromagnetics Society

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INTRODUCTION

Recent decades have been marked by great changes in our electromagnetic field (EMF) environment. The electromagnetic spectrum comprises the range of electromagnetic radiation characterized by their frequencies or wavelengths. It ranges from low to high frequencies, which results in different categories of EMF that range from static and extremely low-frequency fields to gamma rays. The higher the frequency, the shorter the wavelength and greater the energy per photon. Therefore, those that have more energy that can knock electrons out of an atom and then ionize it are harmful and constitute a group of ionizing radiation (UV, gamma, beta, X-ray, etc.), while the other groups with insufficient energy to ionize molecules are called non-ionizing radiation (0.3–3 Hz to 300 GHz). The debate on the health effects of non-ionizing radiation started with epidemiological studies in the late 1970s. Indeed,

Wertheimer and Leeper [1979] published a paper in which they reported a high incidence of leukemia in children living close to high-voltage power lines and

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exposed to extremely low-frequency magnetic fields (ELF-MFs). Since that time, many studies have been published dealing with the effects of ELF on biological functions and health [Selmaoui and Touitou, 1999; Touitou et al., 2010; ANSES, 2013; FDA, 2020].

Concerning radiofrequencies (RFs), several technologies are using EMF, including wireless communication associated with mobile phones, Wi-Fi, etc. The most commonly used tools for wireless communications are mobile phones. Indeed, the International Telecommunication Union (ITU) has reported an estimated 7.74 billion mobile phone subscriptions worldwide in 2017 [ITU, 2018].

The intensive use of these technologies has led to the exposure of the human body to RFs of different signals varying from the second (2 G) to the fifth-generation (5 G). The more recent the wireless generation, the higher the frequency. Public concerns about possible human health risks from exposure to these RFs have led many scientists to generate numerous scientific studies on the effects of human exposure to these man-made EMFs.

A well-known effect is increased body temperature and tissue damage due to heating from absorbed EMF energy. This is called “thermal effects” [ICNIRP, 1998, 2020]. The specific absorption rate (SAR) in W/kg or power flux density (W/cm^2) describes the interaction of RFs with the human body. The threshold for which the effect has been observed was 4 W/kg, leading to the behavioral disruption of animals. To protect the public from the thermal effects of RF, the ICNIRP has issued guidelines on exposure limits using safety factors (50 times less from the threshold for the general public and 10 times less for the occupational situation [ICNIRP, 1998, 2020]). However, the debate continues on non-thermal biological effects in long-term exposure for values below regulatory limits.

A large number of reports then looked at the non-thermal effects of exposure to RF on cancer while others dealt with physiological functions [van Rongen et al., 2009; Ghosn et al., 2012, 2015], endocrine system, fertility, genotoxicity [Saliev et al., 2019; Vijayalaxmi and Prihoda, 2019], sleep [Danker-Hopfe et al., 2016; Lowden et al., 2019], etc. Many models have been used, ranging from cell cultures and in vivo effects of exposure on laboratory animals to clinical and epidemiological studies.

There are many reviews in the literature dealing with the effect of RF-EMF on the brain. However, review papers on the endocrine system, such as melatonin and/or cortisol, are scarce. We found, therefore, that it was worth looking at the biological effects of RF, if any, on the endocrine system. In this review, we will focus on the effects of RF-EMF on two hormones considered as

endocrine markers: melatonin, which is secreted by the pineal gland, and cortisol produced by the adrenocortical gland.

In this paper, both human and animal studies were reviewed. Studies in humans used noninvasive methods to record or collect substrates of the targeted variables. And these variables were used as markers to study some physiological functions in the body. However, animal studies offer a deeper understanding of the mechanistic pathways. Sometimes the extrapolation of animal studies to human studies is very complex but enables us to make a parallelism between the effect observed in animals and humans. That is why these two types of studies are complementary and necessary.

RATIONALE FOR STUDYING MELATONIN AND CORTISOL

Melatonin is produced mainly in the pineal gland. The pineal gland is stimulated by darkness to secrete melatonin and is inhibited by light, thereby showing a circadian rhythm characterized by higher plasma levels at night around 02–04 h and low concentrations during the day [Selmaoui and Touitou, 2003; Touitou et al., 2017]. This nighttime secretion by the pineal gland happens in most of the species that have been studied. The production of melatonin is controlled by the light/dark cycle: exposure to light at night blocks the secretion of this hormone via the retina. Indeed, the pineal gland is a neural structure related to the visual system, including retinohypothalamic connections to the suprachiasmatic nuclei (SCN). The SCN contains the internal biological clock that is important in the generation of circadian rhythms. Exposure to light in the evening can delay the phase of the internal clock, whereas exposure to light in the morning phase advances the clock [Lewy, 2008]. This phase response curve of melatonin to light, which corresponds to different responses according to the timing of exposure to light, is used in the treatment of desynchronized patients (e.g. seasonal disorders and shift workers), either by light or by the administration of chronobiotics at the right time to counteract and combat the circadian misalignment of these patients in setting the internal clock to the correct time [Touitou and Bogdan, 2007; Lewy, 2010].

Melatonin is a pleiotropic hormone with several physiological and pharmacological effects: it is, among others, a synchronizing agent (chronobiotic), a free radical scavenger, and an oncostatic agent. It is a regulator of the sleep-wake rhythm, immune system, neuroendocrine rhythms, or circadian variation of body temperature [Cipolla-Neto and Amaral, 2018]. Some diseases have been reported to be accompanied by a plasma

decrease of the hormone or a disruption of the circadian rhythm of plasma melatonin in humans like in seasonal affective disorder (SAD) [Lewy, 2008; Carpenter et al., 2017], in diseases with neurobehavioral disturbances, such as those seen in autism [Tordjman et al., 2012, 2014] or in cancer [Touitou et al., 1995, 1996].

Since plasma melatonin levels have been found to decrease with age [Touitou et al., 1981], the assumption was made that insomnia, sleep deficiency, and shorter sleep time in elderly people are correlated with the decrease of endogenous melatonin concentrations. Melatonin effects were therefore looked at in insomnia and other sleep disorders, more particularly in elderly people, and melatonin treatment has been shown to be effective in restoring normal sleep and improving quality of life in elderly people (over 55 years of age) [Lemoine and Zisapel, 2012; Zisapel, 2018]. Melatonin administration significantly reduced sleep onset latency, increased sleep efficiency, and increased total sleep duration [Brzezinski et al., 2005].

Concurrently, some individuals, such as electrohypersensitive (EHS) individuals complain of sleep disturbances or other symptoms when they are exposed to EMF [Andrianome et al., 2018], and melatonin was suspected to be disturbed in this population, therefore causing sleep disturbances; but a recent study did not confirm this hypothesis [Andrianome et al., 2016].

In light of the above data, melatonin has been suggested as a potential link between EMF exposure and diseases [Touitou et al., 2006]. This assumption was strengthened by some studies that have reported a decrease of melatonin after exposure to ELF-MF or static magnetic fields [Touitou and Selmaoui, 2012].

Cortisol, a steroid hormone synthesized by the zona fasciculata of the adrenal cortex, is the main glucocorticoid in humans, while corticosterone is the main glucocorticoid produced by rodents. Cortisol is characterized by a circadian rhythm of great amplitude, with a peak at the time of transition between sleep and wakefulness, i.e. between six and eight in the morning; then, the hormone secretion gradually decreases during the day to reach its minimum around midnight, with a progressive re-increase in the secretion from midnight to reach a new peak the next morning between 06 and 08 h. The secretion of cortisol is under the control of the pituitary hormone adrenocorticotrophic hormone, which is controlled by the secretion of the hypothalamic hormone corticotropin-releasing hormone. These peptide hormones have circadian rhythms that precede, in time, the circadian rhythm of cortisol [Krishnan et al., 1990]. Cortisol circadian rhythms may be altered in people working in shift work or night work, with a shift in its peak in relation to the circadian desynchronization experienced by these workers working atypical work hours [Scheer et al., 2019].

Cortisol, like melatonin, is a marker of the circadian temporal structure of an organism.

Moreover, cortisol has many biological effects on various systems of the organism. Its numerous effects include, among others, action on the metabolism of carbohydrates by increasing the synthesis of glucose by the liver (neoglucogenesis), resulting in increased blood glucose levels; suppression of the immune system; action on the metabolism of proteins by stimulating their degradation; action on triglycerides by increasing their synthesis by the liver; action on the bone by inhibiting the intestinal absorption of calcium and the activity of osteoblasts, resulting in the long-run in osteoporosis; immunosuppressive action on circulating B and T lymphocytes, which are decreased; action on the kidney by its mineralocorticoid effect; and finally its anti-inflammatory properties used in therapy. Cortisol, like melatonin, is considered a major marker of the circadian system [Selmaoui and Touitou, 2003]. From a physiological point of view, melatonin and cortisol are two useful marker rhythms that allow us to check the temporal structure of an organism since they both provide evidence for circadian desynchronization, which corresponds to a phase advance, phase delay, or disruption of the circadian clock [Selmaoui and Touitou, 2003; Touitou et al., 2010; Zeitzer et al., 2014].

METHODS

A literature search was performed using PubMed, Medline, Web of Sciences (ISI Web of Knowledge), Google Scholar, and EMF Portal. The keywords for the search was related to the endocrine system and included: “melatonin,” “cortisol,” “corticosterone,” “circadian rhythm,” “pineal gland,” “adrenal gland,” and to EMF-RF, such as “mobile phone,” “cellular phone,” “900 MHz,” “1,800 MHz,” “Wi-Fi,” “2 G,” “3 G,” “4 G,” “GSM,” “UMTS,” and “LTE.” The literature search was carried out until February 2020. The preselection was based on the title and abstract, which allowed us to screen the publications in the English language (or French) and retrieve the relevant ones to the topic of interest. For the EMF criteria, only papers with RF exposure were selected. These were crossed and combined with a search of melatonin (or 6-sulfatoxymelatonin or 6-hydroxymelatonin or pineal gland). For human studies, only laboratory or volunteer studies were included. Epidemiological and observational studies were excluded. Papers with quality issues, such as no full information on dosimetry or experimental protocols, were also excluded. The same search was applied to cortisol or corticosterone. Finally, a detailed review of relevant articles was achieved on a full-text analysis (see Tables 1–4).

TABLE 1. Animal Studies on Melatonin

Authors	Frequencies	Exposure characteristics	SAR or intensity	Species	Endpoints	Results
Vollrath et al. [1997]	900 MHz	15, 30, 60, or 90 min and 2, 4, or 6 h, at day or night	SAR: 0.06–0.36 W/kg for rats and 0.04 W/kg for Hamster (WB)	Rat/Hamster	NAT/Mel (pineal)	No effect
Heikkinen et al. [2003]	900 MHz	1.5 h/day, 5 days/week for 17 months	SAR: 1.5 or 0.35 W/kg (WB)	Mouse	6SM (urine)	No effect
Bakos et al. [2003]	900–1,800 MHz	2 h between 8:00 am and noon for 14 days	SAR: 0.012 and 0.045 W/kg(WB)	Rat	6SM (urine)	No effect
Hata et al. [2005]	1,439 MHz	4 h on 1 day (during the night)	7.5 W/kg for (brain), 1.9 and 2.0 W/kg (WB)	Rat	Mel (pineal)	No effect
Koyu et al. [2005]	900–1,800 MHz	30 min/day, 5 days/week for 4 weeks	SAR: 2 W/kg (WB)	Rat	Mel (serum)	No effect
Sukhotina et al. [2006]	1,800 MHz	7 h	CW, SAR: 8; 80; 800; and 2,700 mW/kg and PW, SAR: from 0 to 2,700 mW/kg	Isolated pineal from Hamster	Mel (pineal)	No effect
Shirai et al. [2007]	1,950 MHz	90 min/day, 5 days/week, for 104 weeks	SAR: 0.67 and 2.0 W/kg (brain and WB)	Rat	Mel (serum)	No effect
Lerchl et al. [2008]	300, 900, and 1,800 MHz	24 h/day for 60 days	SAR: 80 mW/kg (WB)	Hamster	Mel (pineal and serum)	No effect
Qin et al. [2012]	1,800 MHz	2 h/day for 32 days at different moment of the day: 0, 4, 8, 12, 16, 20 after light excitation	SAR: 0.5762 W/kg (WB)	Rat	Mel (plasma)	Decrease, rhythm altered
Kesari et al. [2012]	2.45 GHz	2 h/day for 45 days (between 10 and 17 h)	SAR: 0.14 W/kg (WB)	Rat	Mel (pineal)	Decrease
Kumar et al. [2012]	10 GHz	Continuous for 2 h/day for 45 days	SAR: 0.014 W/kg (WB)	Rat	Mel (serum)	Decrease
Jin et al. [2013]	849–1,950 MHz	45 min/day, 5 days/week up to 8 weeks (between 9 and 14 h)	SAR: 4 W/kg (WB)	Rat	Mel (serum)	No effect
Kim et al. [2015]	915 MHz (RFID)	8 h/day, 5 days/week, for weeks during the nighttime.	SAR: 4 W/kg (WB)	Rat	Mel and 6SM (urine)	Decrease
Cao et al. [2015]	1,800 MHz	Continuous for 2 h/day for 32 days (at 3, 7, 11, 15, 19, and 23 h)	SAR: 0.056 W/kg (WB)	Rat	Mel. Blood samples collected on 5, 9, 13, 17, 21, and 1 h on the following day	Decrease

6SM = 6-sulfatoxymelatonin; CW = continuous wave; Mel = melatonin; NAT = N-acetyltransferase; NG = not given; PD = power density; PW = pulsed wave; RFID = radiofrequency identification; SAR = specific absorption rate; WB = whole body.

ANIMAL STUDIES ON RADIOFREQUENCY EFFECTS

Effects on Melatonin

Animal studies were mostly reported on rats, though some were carried out with hamsters, mice, or cows. Whereas exposure to ELF-EMF was shown to affect melatonin secretion in rats [Selmaoui and Touitou, 1995]

but not in humans [Selmaoui et al., 1996], results from the literature dealing with RF were conflicting and contradictory. Indeed, some of them reported an effect on melatonin secretion, while others found no effect after exposure to RF-EMF (Table 1). Comparisons between data are difficult due to the difference in methodologies, such as the duration of exposure that varied from a few

TABLE 2. Animal Studies on the Corticosterone

Authors	Frequencies	Exposure duration	SAR or intensity	Species	Endpoints	Results
Chou et al. [1992]	2.45 GHz	21.5 h/day for 25 months	SAR: 0.4 W/kg (for 200 g rat) SAR: 0.15 W/kg (for 800 g rat) (WB)	Rat	Corticosterone (plasma)	Changes not replicated
Nakamura et al. [1997]	2.45 GHz	90 min	SAR: 1.8 mW/g to 2.2 W/kg (WB)	Rat	Corticosterone (plasma)	Increase
Imaida et al. [1998]	1.439 GHz	90 min/day, 5 days/week, over 6 weeks	SAR: 0.680–0.453 W/kg (WB)	Rat	Corticosterone (plasma)	Increase
Nakamura et al. [2000]	2.45 GHz	90 min	SAR: 0.40 W/kg PD: 2 mW/cm ² (WB)	Rats	Corticosterone (plasma)	Increase
Shirai et al. [2005]	1.439 GHz	Exposure starting from 5 weeks of age, 90 min/day, 5 days/week, for 104 weeks	SAR: 0.67 and 2.0 W/kg for low and high (brain)	Rat	Corticosterone (plasma)	No changes
Shirai et al. [2007]	1.95 GHz	90 min/day, 5 days/week, for 104 weeks, starting at 5 weeks of age	SAR: 0.67 and 2.0 W/kg (brain/WB)	Rat	Corticosterone (Plasma)	No changes
Li et al. [2008]	2.45 GHz	3 h/day for up to 30 days (between 8 and 11 h)	SAR: 0.2 W/kg (WB) SAR: 0.7 W/kg (brain)	Rat	Corticosterone (plasma)	Increase
Daniels et al. [2009]	840 MHz	3 h/day from day 2 to day 14 after birth	PD: 60 μ W/m ² (WB)	Rat	Corticosterone (plasma)	No changes
Prochnow et al. [2011]	2 GHz	2 h (between 9 and 12 h)	SAR: 2 or 10 W/kg (brain)	Rat	Corticosterone (plasma)	No change
Syednour and Chekaniazar [2011]	900 MHz	3 h/day for 10 or 50/60 days	SAR: 0.6 W/kg (WB)	Hamster	Corticosterone (serum)	Increase
Aldad et al. [2012]	800–1,900 MHz	9 or 15 h/day or for 24 h/day in gestational days (1–17)	SAR: 1.6 W/kg (WB)	Mouse	Corticosterone (serum)	No changes
Bouji et al. [2012]	900 MHz	15 min (between 9 and 12 h)	SAR: 6 W/kg (brain)	Rat	Corticosterone (plasma)	Increase
Pawlak et al. [2014]	900 and 1,800 MHz	9 times during 24 h, 4 min each.	PD: 0.090 to 0.110 W/m ² Embryos exposed (WB)	Broiler flock of Ross	Corticosterone (plasma)	Increase
Ragy [2015]	900 MHz	1 h/day for 60 days	PD: 2.5 mW/cm ² (WB)	Rat	Corticosterone (serum)	Increase
Bouji et al. [2016]	900 MHz	45 min on the experimental days 1–5, 8–12, 15–19, and 22–26 (between 9 and 11 h)	6 W/kg (brain)	Rat	Corticosterone (plasma)	No changes
Kumar et al. [2016]	2.45 GHz	2 h/day for 1 month (from 10 and 12 h)	SAR: 0.019–0.023 W/kg PD: 0.029–0.033 mW/cm ² (WB)	Mouse	Corticosterone (plasma)	Increase
Pawlak et al. [2018]	1,800 MHz	10 times during 24 h, 4 min each	PD: 0.09–0.11 W/m ² (± 0.001 W/m ²)	Chick	Corticosterone (plasma)	Increase

(Continued)

TABLE 2. Continued

Authors	Frequencies	Exposure duration	SAR or intensity	Species	Endpoints	Results
Shahin et al. [2018]	2.45 GHz	2 h/day for 15, 30, or 60 days (from 9 to 11 h)	Embryos exposed (WB) SAR: 0.0146 W/kg PD: 0.0248 mW/cm ² (WB)	Mouse	Corticosterone (serum)	Increase
Perov et al. [2019]	171 MHz (CW)	6 h/day for 15 days (from 8 and 14 h)	SAR: 0.006 W/kg (15, 25, and 35 V/m) (WB)	Rat	Corticosterone (urine)	Increase
Gupta et al. [2019]	900, 1,800 and 2,450 MHz	1 h/day for 28 days (between 10 and 13 h)	SAR: 0.042 W/kg (WB) 0.131 W/kg (Brain)	Rat	Corticosterone (plasma)	Increase
Kalanjati et al. [2019]	2,100 MHz	4 h/day for 30 days	SAR: 0.84–1.86 W/kg (WB)	Rats	Corticosterone (plasma)	Increase

NG = not given; PD = power density; PI = plasma; SAR = specific absorption rate; WB = whole body.

minutes to hours per day and even weeks or months. The SARs used were also different from one study to another. In addition, the time of day when the RF exposure was applied is different between studies and could have an impact on the sensitivity of melatonin production as its secretion is circadian rhythm-dependent. Indeed, some authors have reported a specific effect related to the timing of exposure according to the circadian rhythm. Cao et al. [2015] and Qin et al. [2012] exposed rats at different Zeitgebers of the circadian rhythm. In a study reported by Qin et al. [2012], where animals were exposed at 0, 4, 8, 12, 16, and 20 h, it was shown that the rhythm of plasma melatonin was altered after exposure to RF and that the effect was more prominent in rats exposed to RF at 16 h. Similarly, Cao et al. [2015] exposed rats at different times of the day, such as 3, 7, 11, 15, 19, and 23 h. The authors found that the circadian rhythm of plasma melatonin concentrations was shifted in a group of exposed rats when compared with sham-exposed ones. Also, the plasma melatonin concentrations were significantly decreased when rats were exposed at 23 and 3 h [Cao et al., 2015]. These studies showed clearly that the timing of exposure during the day is likely a factor to take into account the effect of RF on melatonin production.

Another important point to deal with is the control of light, which inhibits melatonin secretion. The length of the light/dark cycle should also be considered in the studies.

Effects on Corticosterone

Corticosterone is the major glucocorticoid of rats and mice [Selmaoui et al., 2003; Yu et al., 2015]. Since most studies on the effect of RF-EMF have been

conducted on rodents (rats or mice), corticosterone levels were determined. Here again, different signals were used (900, 1,800, 1,900, 2,100, 2,400 MHz) and the methods in terms of SAR and duration of exposure were also different. When looking at these studies, we observe that the lowest SAR applied (0.006 W/kg) led to an increase of corticosterone levels in rats [Perov et al., 2019], while some studies with high SARs, such as 6 or 10 W/kg, did not find any effect on corticosterone levels [Prochnow et al., 2011; Bouji et al., 2016]. As we know, the thermal effect has been observed at SAR above 4 W/kg [ICNIRP, 1998, 2020]. In view of this, it could be expected that exposure to 6 or 10 W/kg of RF fields would increase the temperature of the animals, which would cause stress and consequently, an increase in corticosterone levels. Another point of discrepancies in the studies' results is the unreliability of the results with the same SAR and even within the same laboratory. Indeed, Bouji et al. [2012] reported an effect with 6 W/kg on rats' corticosterone levels. These results could not be replicated later in another study [Bouji et al., 2016]. Globally, the results showed an increase in corticosterone concentrations in the blood. Only a few studies did not find any effect. These results should be taken cautiously, for the simple reason that corticosterone is a hormone of stress and its levels can increase with the stress generated by different factors. One of the factors of stress in the laboratory is the handling of animals.

HUMAN STUDIES ON RADIOFREQUENCY EFFECTS

Effects on Melatonin

With regards to controlled human studies, there were only a few experiments that have been performed

TABLE 3. Human Studies on Melatonin

Authors	Frequencies	Exposure characteristics	SAR or intensity	Population size and gender	Endpoints	Results
Mann et al. [1998]	900 MHz	8 h (during night)	PD: 0.02 mW/cm ² (head)	<i>N</i> = 24 males (age = 18–37)	Mel in serum (every 20 min from 23 to 7 h)	No effect
de Seze et al. [1999]	900 and 1,800 MHz	2 h/day for 5 days for 4 weeks (from 14–16 h to 16 h 30 min–18 h 30 min)	SAR: 0.3 W/kg (head)	<i>N</i> = 19 males (age = 20–32)	Mel in plasma (hourly at night and every 3 h during the day)	No effect
de Seze et al. [2001]	900 MHz	2 h/day for 5 days for 4 weeks (from 14–16 h to 16 h 30 min–18 h 30 min)	Power: 0.25 W (head)	<i>N</i> = 30 males (age = 18–40)	Mel in plasma (hourly at night and every 3 h during the day)	No effect
Radon et al. [2001]	900 MHz	Twenty 4 h sessions (day-time and night-time)	SAR: 0.025 W/kg (head)	<i>N</i> = 8 males (age = 20–30)	Mel in saliva (every 30 min)	No effect
Bortkiewicz et al. [2002]	900 MHz	60 min (from 19 to 20 h)	SAR: 1.23 W/kg (head)	<i>N</i> = 9 males (age = 19–29)	6SM in urine (19 h, midnight and 7 h)	No effect
Jarupat et al. [2003]	1,900 MHz	30 min/h for 6 h (from 19 to 1 h)	SAR: 0.68 W/kg (head)	<i>N</i> = 8 females (age = 16–36)	Mel in saliva (at 19 and 2 h)	Decrease in saliva at 2 h
Wood et al. [2006]	895 MHz	30 min (prior to sleep)	SAR: 0.674 and 0.11 W/kg (head)	<i>N</i> = 55 (30 males, 25 females) (age = 18–60)	6SM in urine (overnight)	No effect

6SM = 6-sulfatoxymelatonin; Mel = melatonin; NG = not given; PD = power density; SAR = specific absorption rate.

to investigate the effect of mobile phone RF-EMF exposure on melatonin and cortisol. This scarcity of research could be due to ethical reasons. Indeed, experiments with human subjects occur only in the context of a clear scientific rationale and only with subjects who volunteered to participate. Studies with healthy volunteers are practically using noninvasive sampling to record or collect substrates of the targeted variables. Nowadays, in addition to blood, saliva and urine are becoming very convenient substrates that are easy to sample and in which many analyses can be performed.

All of these studies were carried out with healthy participants and used mobile phones or base station-like exposures with levels less than the ICNIRP's RF exposure limit; however, only one study has reported an effect while others did not. It is important to emphasize that the observed effect could be due to chance as a result of a small number of participants [Jarupat et al., 2003] (*n* = 8). Also, the use of urinary excretion data or blood and salivary single samples for melatonin that is secreted in a circadian manner can complicate interpretation; i.e. information regarding a possible phase shift in melatonin production could be missing.

Two studies were designed to look for the effect of mobile phone RF on the circadian rhythm of melatonin levels [Mann et al., 1998; de Seze et al., 1999]. In short, Mann et al. [1998] exposed volunteers during the

nighttime from 23 to 07 h to 900 MHz RF while the subjects were sleeping. Blood samples were collected every 20 min, from 23 to 07 h. The nocturnal pattern of serum melatonin of the exposed session was compared with that of the sham session. Even if the circadian rhythm of serum melatonin was not assessed as a whole, it is assumed that any potential effect on the circadian rhythm of melatonin levels would be observed in the nocturnal secretion of this hormone, as its higher amplitude and secretion occur during the nighttime. Therefore, the study is considered quite indicative of any effect of RF on the circadian rhythm of melatonin levels that could occur. In de Seze et al.'s study [1999], participants were sampled hourly during the night and every 3 h during the day. They were exposed to 900 or 1,800 MHz for 2 h per day. Exposure periods were in the early or late afternoon (14–16 h or 16 h 30 min–18 h 30 min).

Both studies reported no statistically significant effect of exposure on nocturnal serum melatonin. Those studies were interesting in terms of the physiological function studied, which looked at the effect of RF on the circadian rhythm of melatonin secretion. However, the study by de Seze et al. [1999] was weakened by the fact that it was not performed in the blind and that exposure was outside of the period of phase response, and an effect could occur during this time period. Similarly, human exposure to GSM 895 MHz of mobile phone signal was

TABLE 4. Human Studies on Cortisol

Authors	Frequencies	Exposure characteristics	SAR or intensity	Population size and gender	Endpoint	Results
Mann et al. [1998]	900 MHz	8 h (during night)	PD: 0.02 mW/cm ² (head)	<i>N</i> = 24 males (age = 18–37)	Cortisol (serum) (every 20 min from 23 to 7 h)	Transient effect
de Seze et al. [2001]	900 MHz	1–2 h/day for 5 days for 4 weeks (from 14–16 h to 16 h 30–18 h 30)	SAR: 0.25 W/kg (head)	<i>N</i> = 30 (age = 18–40)	Cortisol (plasma) (hourly at night and every 3 h during day)	No effect
Radon et al. [2001]	900 MHz	Twenty 4 h sessions (day-time and night-time)	SAR: 0.025 W/kg (head)	<i>N</i> = 8 males (age = 20–30)	Cortisol (saliva)	No effect
Braune et al. [2002]	900 MHz	50 min (afternoon)	SAR: 0.84 W/kg (head)	<i>N</i> = 40 (20 males) (age = 20–34)	Cortisol (serum) (every 10 min)	No effect
Djeridane et al. [2008]	900 MHz	2 h/day for 5 days/week for 4 weeks (from 14–16 h to 16 h 30 min–18 h 30 min)	SAR: 0.3 W/kg (head)	<i>N</i> = 20 males (age = 20–32)	Cortisol (hourly at night and every 3 h during day)	Effect with 2 W
Augner et al. [2010]	900 MHz	50 min (different moments of the day)	PD: 5.2, 153.6, and 2126.8 mW/m ² (WB)	<i>N</i> = 57 (60% males) (age = 18–67)	Cortisol (saliva)	No effect
Ghosn et al. [2015]	900 MHz	26 min (morning and afternoon)	SAR: 0.49 W/kg (head)	<i>N</i> = 26 (13 females) (Mean age = 23.5)	Cortisol (saliva) (before and after exposure)	No effect

PD = power density; SAR = specific absorption rate.

conducted by Wood et al. [2006] on a large number of volunteers (55 adult males and females). Melatonin was analyzed in urine as 6-sulphatoxymelatonin (6SM) during the night. The results showed that the total concentration of 6SM during the night did not differ between the two exposure conditions. Overall, based on the data reported in Table 3, it appears that RF fields did not affect melatonin in humans.

Effects on Cortisol

Very few studies have been conducted on cortisol. Unlike animal studies, human studies generate very minimal or almost no stress, especially since the methods for collecting samples where cortisol is analyzed are increasingly noninvasive (urine and saliva). Most studies have been conducted with GSM signals and some have measured cortisol during nighttime exposure [Mann et al., 1998]. The authors reported no significant effect of RF on cortisol. However, there was an indication of interaction between exposure and time, meaning that the patterns of cortisol serum concentration differed between the GSM and sham conditions. By comparing the respective 1-h segment of the two conditions, slightly higher cortisol levels were observed during the first hour and last hour of exposure. Similarly, Radon et al. [2001] did not find any effect on salivary cortisol of a GSM-like signal transmitted by an antenna. In this study, the

participants underwent both daytime and nighttime exposures. As noted above, the small sample was a limitation of the study. Another study aiming to investigate the EMF exposure effect on vasoconstrictor activity [Braune et al., 2002] exposed female and male volunteers to a signal from a GSM 900 MHz mobile phone. Blood was collected first after an initial resting phase immediately before exposure and subsequently every 10 min. Cortisol serum levels were measured for each participant. No data indicated that exposure to RF-EMF emitted by mobile phones for up to 50 min had any effect on the tested hormone levels. Other authors [Djeridane et al., 2008] have evaluated the effect of the 900 MHz GSM mobile phone RF on the circadian rhythm of steroids and pituitary hormone levels in healthy men. This study has been performed on a circadian basis. Indeed, blood was sampled hourly during the day and every 3 h during the night. Four sessions have been scheduled for the blood sampling spaced in 2-week intervals: one session during the pre-exposure period, two sessions within the exposure period, and one in the postexposure period. The results did not show any effect of mobile phone RF on the circadian rhythm of cortisol levels. However, it was missing a sham exposure, and the experiment was not performed in the blind. Another study [Augner et al., 2010] has investigated whether GSM 900 MHz base station signals may have an effect on salivary cortisol levels. The authors used different types of

shielding, and three different exposure levels were obtained. The power density was measured during the exposure sessions, and the average values were calculated for each condition: high ($2126.8 \mu\text{W}/\text{m}^2$), medium ($153.6 \mu\text{W}/\text{m}^2$), and low ($5.2 \mu\text{W}/\text{m}^2$). Fifty-seven participants were randomly assigned to receive one of three exposure scenarios, each consisting of five 50-min exposure sessions separated from each other by 5-min intervals. Different scenarios were realized. Globally, analysis of variance showed no difference between the three scenarios and no interaction between the scenario and session number. The low number of participants in the control scenario is a limiting factor for this analysis. Recently, Ghosn et al. [2015] aimed to investigate the effects of GSM mobile phone RF exposure on electroencephalogram (EEG), while the salivary cortisol level was also assessed. For each individual, the sessions were either in the morning or in the afternoon. Salivary cortisol samples were taken before and after the exposures; no significant effect of exposure was observed.

Overall, these studies on the effects of RF on cortisol production did not report consistent changes in human cortisol levels.

CONCLUSIONS

This review paper shows that there is no consistent evidence on the effect of RF-EMF on the secretion of melatonin as one study reported an effect while others did not. It is worth noting that for animals, older studies found no effect, while more recent studies found an effect. It is known that recently, dosimetry tools have become more reliable and exposure systems are more efficient, which could probably be a factor in the outcome of the results. In any case, this deserves special attention and a detailed comparative study. Although direct effect of RF-EMF exposure on melatonin has not been confirmed, several studies in the literature reported a potential protective effect of melatonin against the adverse effects induced by RF-EMF exposure, such as oxidative stress [Kerman et al., 2005; Ozguner et al., 2005a; Köylü et al., 2006; Ozguner et al., 2006; Sokolovic et al., 2008; Kesari et al., 2012; Naziroğlu et al., 2012; Aynali et al., 2013; Sokolovic et al., 2013; Meena et al., 2014; Oksay et al., 2014; Tök et al., 2014; Djordjevic et al., 2015; Sokolovic et al., 2015; Gumral et al., 2016; Pandey and Giri 2018], DNA damage [Lai and Singh, 1997; Liu et al., 2013; Sokolovic et al., 2015; Pandey and Giri, 2018], neuroprotective effects [Erdem Koc et al., 2016], histopathologic changes in skin [Ayata et al., 2004; Ozguner et al., 2004], and adverse effects of EMF on the kidneys [Oktem et al., 2005; Ozguner et al., 2005b; Ulubay et al., 2015] or liver [Gökcimen et al., 2002]. Even though melatonin secretion is not

affected by RF-EMF exposure, it seems to play an important role in the protection of the organism from oxidative stress induced by RF-EMF exposure. One could argue that co-exposure to RF-EMF with another factor that could disturb or suppress melatonin secretion, like light, would promote oxidative stress. It is also well-known that oxidative stress accelerates aging [Cabello-Verrugio et al., 2017] and contributes to cancer development in humans [Helfinger and Schröder 2018], among other diseases.

Concerning animal corticosterone concentrations, data have shown that most studies reported an effect of RFs on this hormone. However, it should be noted that corticosterone is the hormone of stress in animals; therefore, the handling of animals will implicitly generate stress that may affect the secretion of corticosterone. To overcome this problem, some special practices are required, such as the habituation of animals to continuous human handling before the test. From this review on RF effects on cortisol and melatonin, it appears that scientific papers in the literature are conflicting: showing effects, no effects, or inconclusive data. This implies the need for additional research on a higher number of subjects and for protocols to be perfectly controlled with follow-up studies to better determine whether the chronic effect of RF on the biological functioning and health of users exists or not.

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