ANALYTICAL REVIEWS

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Review

SYSTEMIC EFFECTS OF RADIOFREQUENCY ELECTROMAGNETIC FIELDS (REVIEW). PART 1. SECRETION GLANDS

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Among publications on systemic effects of radio frequency electromagnetic fields (RF EMF), primarily those inherent in cellular communication devices (most often from 900 MHz to 2.5 GHz), as well as Wi-Fi, special attention should be paid to their influence on structural changes in the secretory glands, which are often direct targets for the impact of the corresponding RF EMF (for example, the thyroid gland).

Various pathohistological effects of chronic exposure to RF EMF in different modes on the glands of external secretion have been established both in experimental studies on animals and in epidemiological ones. The parotid gland, salivary glands, sweat glands are among those mentioned in them.

The endocrine glands can also be affected by RF EMF, which is confirmed by the results of numerous studies on the pineal gland, pituitary gland, thyroid gland, and adrenal glands, in which changes in their structure and functions have been recorded in both experimental animals and humans. At the same time, there is fairly pronounced dependence between resulting effects and exposure and other characteristics of RF EMF.

At present, biological effects of RF EMF produced by various frequency ranges (cellular devices and telecommunication masts) have been reliably established. Various histopathological changes have been registered in the glands of mixed secretion such as the liver, pancreas, testicles and ovaries. Serious disorders in the testicles and ovaries revealed in experimental animals are particularly relevant since they undoubtedly lead to reproductive dysfunction.

Particular concern is raised by the fact that cellular users of different ages, primarily children and adolescents, carry mobile devices in their trouser pockets, i.e. in close proximity to the sex glands.

The present period is also characterized by accumulation of comparative epidemiological data as well as non-invasive measurements of structural and functional changes in the secretory glands in humans. Based on them, an unambiguous conclusion should be made about the need to limit and take precautions when using cellular devices, which is also indicated by some of the works considered in this review.

Keywords: *electromagnetic fields of the radio frequency range, cellular devices, Wi-Fi, endocrine glands, exocrine glands, mixed secretion glands, histological changes, young animals.*

The glands of external secretion. Negative effects produced by radio frequency electromagnetic fields (RF EMF) on brain structures can be considered quite proven [1]. Given that, we can assume that RF EMF radiation of mobile phones can also 'affect' secretion glands, the ***parotid gland*** in particular.

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Although very few studies have been published on the subject, a work by S. Sadetzki et al. reported an increased risk of the parotid gland cancer in mobile phone users [2]; experiments conducted by Z. Ozergin Coskun et al. established histopathological changes in rats' parotid upon exposure to 1800 MHz for 6 and 12 hours a day, namely, an increase in the apoptotic index, which was more prominent upon longer exposure [3]. Dependence between the level of histopathological changes and duration of exposure to 2100 MHz RF EMF (6 hours/day, 5 days/week, for 10 or 40 days) was established in a study by F. Aydogan et al. Histological changes in salivary glands (acinar epithelial cells, interstitial space, ductal system, vascular system, nucleus, amount of cytoplasm and variations in cell size) were found to be more prominent upon longer exposure (40 days) [4].

Moreover, salivary dysfunction (lesser salivary secretion) was established both in people aged 18–30 years and 30–60 years, who lived approximately one kilometer away from mobile base stations for not less than 8 years [5].

The fifth generation mobile communication 5G potentially employs two frequency bands, 600–60 000 MHz and 24–100 GHz (4.8–4.99 GHz and 24.25–24.65 GHz in Russia). Yu.G. Grigoriev believes that active implementation of such communication networks "…can create much higher hazards associated with constant radiation exposure of new critical organs, such as skin and eyes" [6]. Underestimation of these health risks can be fatal.

Thus, K. Karipidis et al. claim in their review [7] that available results, in particular those obtained by epidemiological studies, provide little evidence of a relationship between low-level millimeter wave band and any hazardous health effects since the related exposures are well below their permissible limits stipulated by the International Commission on Non-Ionizing Radiation Protection (ICNIRP). However, this point of view is strongly criticized by S. Weller et al. since it sends the wrong messages regarding safety assessment and public health [8].

Since eye sclera and skin are considered new critical organs upon exposure to the millimeter band, we can assume multiple ***sweat glands*** to also be affected by RF EMF.

In this respect, studies by S.R. Tripathi et al. [9] and N. Betzalel et al. [10] are of interest. By using optical coherence tomography, the authors established the tips of the sweat ducts to have a helical structure so they could be considered a helical antenna. The resonance frequency of this antenna in the axial mode of operation lies in the THz wave region with a center frequency of 0.44 ± 0.07 THz [9], which may lead to a high specific absorption rate (SAR) of the skin in extremely high frequency band [10].

In addition, it was established through experiments that human skin reflectance in sub-terrahertz (sub-THz) band, which is being actively promoted on the market by mobile operators (5G in particular), depends on perspiration intensity and correlates not only with levels of stress in a given person but also ECG parameters. In this relation, it is necessary to consider possible outcomes for public health due to unrestricted use if sub-THz technologies such as 5G [10] as well as new 6G bands.

We believe that all foregoing evidence should be taken into account when new mobile communication technologies are widely implemented into practice since human skin becomes a new critical organ in this case. Considering the exposure area (1.5–2 m^2 in an adult person), this can become not a potential but rather an obvious health threat for humans, primarily children and adolescents as a population cohort, which is the most sensitive to any external exposures.

The endocrine glands. As stated above, negative effects of RF EMF on brain

structures can be considered well proven [1]; therefore, such endocrine glands as ***epiphysis*** (the tectal plate in the midbrain) and ***hypophysis*** (the interbrain) can also be affected by them. The results obtained by studies outlined below are evidence of this impact.

Effects on the ***epiphysis*** are reported in a study by S.G. Yashchenko and S.Yu. Rybalko conducted on young rats. They investigated impacts exerted by RF EMF of up-to-date communication devices such as personal computers (PC) (4h/day, for 26 weeks) and mobile phones (MP) (925 MHz, each 5 minutes for 12 hours for 26 weeks, power flux densities (PFD) reached 97.8 μW/cm^2 in the cell center with the mean integral value being 22 μW/cm^2). The authors established changes in the epiphysis tissues ultrastructure involving development of general specific morphological changes for each exposure type, PC and MP. Their findings give evidence of negative effects produced by RF EMF on the epiphysis [11].

Use of electrophotography image or gas discharge visualization after 15-minute exposure to MP for students (aged 17.40 ± 0.24 years) established significant reductions in subtle energy levels in several organs (pancreas, thyroid gland, cerebral cortex, cerebral vessels, left ear and left eye, liver, right kidney, spleen and the immune system), ***hypophysis*** included [12].

At present, smartphones are being commonly used as a new mobile phone generation; the gadget antenna is located at its bottom and it has created a new exposure type that involves greater electromagnetic effects on the neck. It is evidenced by estimated distribution of absorbed doses in this area and the ***thyroid gland*** becomes a new critical organ in this case [13, 14].

Various changes in the thyroid structure and function as well as changes in hormone levels upon exposure to RF EMF have been summarized in several reviews [15, 16], including those focusing on children and adolescents [14].

In addition, ***experimental studies*** established histological and biochemical changes in thyroid cells in rats and mice upon exposure to RF EMF within band between 900 MHz and 2.45 GHz. Experiments on young rats revealed a decline in cuboid cells, follicular colloid fluid and follicle sizes upon exposure to MP RF EMF (900 MHz, 10 minutes, 12 times a day for 1 month) [17]; formation of apoptotic bodies and increased caspase-3 and caspase-9 activities in thyroid cells of the rats were found upon exposure to impulse-modulated RF fields (900 MHz, modulation equal to 217 MHz, 20 min/day, for 2 months) [18].

Exposure to RF EMF created by MP with double transceiver 900/1800 MHz (50 calls 30 sec each with 15-second breaks between them for 8 weeks) led to a decrease in colloid content in microfollicles, wider connective tissue septa and more dilated blood capillaries [19].

A diathermy model was employed by M.J. Misa-Agustiño et al. to investigate effects of 2.45 GHz on rats' thyroid with maximum exposure in the left front leg. Exposure to RF EMF was single (30 min/day, 3 and 12 W) or repeated (30 min/day, 3 W, for 2 weeks). Morphometric measurements in thyroid tissue were conducted 90 minutes and 24 hours after the last exposure in all experimental groups. The authors did not find any signs of apoptosis in thyroid cells or any changes in septa width in the central part of connective tissue; however, they established certain changes in the size of central and peripheral follicles, which indicate developing hypertrophy of the gland related to exposure intensity and / or number of exposures [20].

Studies with participating children and adolescents as well as people younger than 25 years have revealed a wide range of changes in the thyroid gland upon exposure to RF EMF.

At present, RF EMFs created by base mobile stations are known to be able to produce negative effects on hormone levels in people living in close proximity to them. In particular, a study by E.F. Eskander reported changes in hormone levels in dynamics established for young males/men and young females/women (aged 14–22 years and 25–60 years respectively) as an exposure period grew longer (1, 3, and 6 years); all participants lived not farther than 500 meters away from a base station. The greatest changes were found for the 6-year exposure such as a significant decline in the thyroid hormones, both serum thyroxin (T4) and triiodothyronine (T3), and adrenocorticotrophic hormone (ACTH) in all groups, and in the sex hormones (declining testosterone levels in young males/men, declining serum prolactin levels in young females but growing levels of the hormone in adult women) [21].

To investigate effects of MP RF EMF on the human thyroid gland, researchers analyze hormone levels [22], conduct clinical examinations [23] and US-examinations with simultaneous surveys involving use of various inventories.

Thus, a survey conducted among 77 students with different MP use, 5–20 min/day and more than 120 min/day together with hormone level analysis established a higher than normal TSH level, low mean T4 and normal T3 concentrations in mobile users; the changes were the most prominent in active users [22].

Similar studies were conducted by N.M. Baby et al. with 83 participating students (aged 18–25 years). On average, 53 % of the respondents talked on the mobile phone for 0.5 hours/day; 28.9 %, 1.5 hours/day; 10.8 %, 3.5 hours/day. Clinical examination of the thyroid revealed that 13.6 % of the participants had thyroid swelling, 3.6 % had symptoms of thyroid dysfunction and 3.6 % had both thyroid swelling and symptoms of thyroid dysfunction. A significant correlation was also found between total radiation exposure and an increase in TSH in both groups [23].

A prospective study aimed at investigating MP RF EMF effects on the thyroid was done by N.M. Elsayed et al. on 180 participants, 110 females and 70 males, ranging in age from 15 to 65 years. US examination revealed 46.7 % of the participants to have abnormal findings of the thyroid gland, more frequently in smartphone users and in females. Multinodular goiter was the most common abnormality (54 %) [24].

Statistical reports on the population incidence of endocrine, nutritional and metabolic disorders in the Russian Federation give evidence of a significant increase in the number of children and adolescents suffering from these diseases since 2000: 2.8 times for the age group of 0–14 years and 5.5 times for the age group of 15–17 years [14].

Basic structures of the ***thymus***, in particular in rats, are known to be still forming in the postnatal period [25]. Therefore, RF EMF effects can be quite drastic in this period as evidenced by sporadic studies conducted on young rats.

Thus, exposure to 900 MHz (1 hour/day, for 22–59 days after birth) led to histopathological changes in the thymus tissue: extravascular erythrocytes were observed in the medullary/corticomedullary regions [26]. A study involving acute (1 week) and repeated (10 weeks) exposure to RF EMF of young rats in two frequency bands (900 and 2100 MHz, 2 hours/day) established greater expression of caspase 3 and 12, glucose-regulated protein 78 kDa (Grp78), C/EBP and homologous protein, which indicates increased levels of ER stress pathway proteins and could cause apoptosis of the thymus cells [27].

M.J. Misa-Agustiño et al., just as they did when investigating RF EMF effects on the thyroid, used a diathermy model to examine effects of 2.45 GHz (power equal to 1.5, 3.0 or 12.0 W, 30 min/day for 1 and

10 weeks) on young rats' thymus. The study found increased distribution of blood vessels (more prominent in the medulla) along with the appearance of red blood cells and hemorrhagic reticuloepithelial cells in animals exposed to 12.0 W (SAR per 1 gram of the thymus tissue is 0.482 ± 12.10^{-3} W/kg). The effect here depended solely on the exposure power and not its duration. Moreover, the authors found a relationship between exposure to RF EMF and greater endothelial permeability and vascularization of the thymus [28].

Established histopathological changes in experimental animals' thymus upon exposure to RF EMF may well be found in people who are active mobile phone users and tend to keep their phones in breast pockets. Still this assumption requires further investigation.

Hormones released by the ***adrenals*** are known to maintain homeostasis and support adaptation to various physiological and emotional situations. However, there are only sporadic studies that concentrate on investigating RF EMF effects on the adrenals.

We managed to find only two available publications, A. Kocaman et al. and S. Shahabi et al. Both studies were conducted on young Wistar rats exposed to 900 MHz EMF.

A. Kocaman et al. detected a significant increase in the mean volume of the adrenal gland upon exposure to RF EMF 60 minutes/day fir 15 days [29]. The study by S. Shahabi et al. involved more intensive RF EMF exposure (6h/day, for 4 and 8 weeks respectively); as a result, it was established that the fasciculata layer of adrenal cortex eventually thickened. While the number of cells in zona fasciculata remained constant, the cell size and perimeter increased during RF EMF exposure. The outlined changes were more prominent upon the 8-week exposure [30].

Since negative changes were detected both in the hypophysis [12] and adrenals as stated above [29, 30], we can assume that RF EMF affects the hypothalamic-pituitary-adrenal axis, a neuroendocrine system responsible for maintaining homeostasis, adaptation to external factors and survival under stress. This, in its turn, can lead to various systemic responses to RF EMF exposure.

The glands of mixed secretion. This group includes such glands as the liver, pancreas, and sex glands, namely, testicles in males and ovaries in females.

However, very few publications are focused on investigating RF EMF effects on the liver and testicles and only sporadic ones concentrate on effects on the pancreas and ovaries.

In particular, upon exposure to 900 MHz (1, 2 and 4 h/day for 30 days), M. Sepehrimanesh et al. did not establish any significant histopathological changes in the ***liver*** [31]. However, such changes were detected by H.R. Ma et al. [32] and D.Ö. Okatan et al. [33] even upon shorter exposure to RF EMF.

In the first case (4 h/day for 18 days), the histopathology examination showed diffuse hepatocyte swelling and vacuolization, small pieces and focal necrosis [32]; in the second case (1 h/day for 24 days), occasional irregularities in the radial arrangement of hepatocytes, cytoplasmic vacuolization, hemorrhage, sinusoid expansion, hepatocyte morphology and edema [33].

Daily exposure of adult mice to RF EMF created by the two-band Nokia 1112 (900/1800 or 950/1900 MHz) 1 h/day for 10 days induced inflammatory cellular infiltration and the hepatocytes appeared vacuolated and contained denser nuclei. Upon exposure duration being 12 h/day, liver sections of group three showed more intensive inflammatory response around the central vein whereas hepatocytes were swollen and their cytoplasm appeared to be highly vacuolated [34].

Effects of exposure to 2.45 GHz are different from those produced by exposure to 900 MHz. Histopathological studies by

K. Holovská et al. (3 h/day for 3 weeks) did not established any changes in hepatocyte structure; however, electron microscopy of hepatocytes revealed vesicles of different sizes and shapes, lipid droplets, and proliferation of smooth endoplasmic reticulum as well as presence of necrotic hepatocytes. In addition, the authors found moderate hyperemia, dilatation of liver sinusoids, and small inflammatory foci in the center of liver lobules [35]. Completely distorted liver architecture and elongated nuclei with cytoplasm of some hepatocytes were found in a study by P. Chauhan et al. (2 h/day for 35 days) [36].

Later, E.A. Adebayo et al. established pronounced dilated sinusoids, distorted architecture, hyperchromatic nuclei, and congested central vein with change of hepatocytes structure in rats kept 24 meters away from the base of two different telecommunication network masts (1800 MHz) for 5 weeks (1.40 W/cm^2) [37].

Therefore, exposure to RF EMF created by both mobile phones and base stations can induce histopathological changes in liver tissues of experimental animals.

Negative histopathological changes have also been established in ***testicle*** tissues.

Thus, grossly distorted seminiferous tubules and epididymis with loss of cellular structure and an area of inflammatory changes with complete absence of spermatozoa, which may lead to low fertility, were found in rats kept 24 meters away from telecommunication network masts (1800 MHz) for 5 weeks [37].

Upon exposure to 900 MHz RF EMF (1 h/day for 30 days), exposed male rats had vacuoles in seminiferous tubules basal membrane and edema in the inter-tubular space. Seminiferous tubule diameters and germinal epithelium thickness were both smaller, and apoptotic index was higher [38].

M. Saygin et al. detected a declining quantity of Leydig cells, testis cell degeneration and apoptosis in rat testicle tissue upon exposure to 2.45 GHz (60 min/day for 28 days) [39]. P. Chauhan et al., having simulated repeated RF EMF exposure (2.45 GHz, 2 h/day for 35 days) revealed epididymis epithelium degeneration and tube necrosis, lumen occlusion, and smaller testicular tubule size [36].

In our opinion, special attention should be paid to investigating outcomes of exposure to Wi-Fi (2.24 GHz, 1 h/day and 7 h/day for 2 months). As a result, the number of apoptosis-positive cells and caspase-3 activity increased in the seminiferous tubules of exposed rats and this was more prominent upon daily 7 h/day exposure. Upon 1h/day exposure, the testicular tubule architecture and interstitial tissue remained unchanged and germinal testis epithelium was undamaged. On the contrary, 7-hour exposure led to both fewer layers of embryo cells and lower mean testis score [40].

Histopathological changes in female rats' ovaries were established upon exposure to 1800 MHz (2 h/day for 30 and 60 days respectively). After 30 days, stagnation and fewer quantities of follicles were found in the ovaries; after 60 days, degeneration of pre-ovulatory follicle cells and macrophage infiltration were added and vacuolization of interstitial cells and granulose cell layers was activated [41].

Based on all foregoing, we can state that exposure to RF EMF of various frequency bands induces considerable histopathological changes in testis and ovary tissues. We believe the matter deserves special attention since many mobile phone users (especially often children and adolescents) tend to keep their mobile phones / smartphones in trousers' pockets.

The only study that reported negative effects on RF EMF on several organs and tissues, the ***pancreas*** included, was published by H. Bhargav et al. In this study, a statistically significant decline in subtle energy levels was detected using electrical photonic visualization in ***61 adolescents*** (the

average age was 17.40 ± 0.24 years) after 15-minute exposure to mobile phone EMF on the right year [12].

Conclusion. To sum up, we can state that most analyzed studies reported not only functional but also variable histopathological changes in secretion glands, their tissues and cells. We believe that these results obtained by investigating exposure to RF EMF of various frequency bands on the glands of external, internal and mixed secretion provide convincing evidence of their negative effects including those produced on children and adolescents.

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