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Influences of exposure to 915-MHz radiofrequency identification signals on serotonin metabolites in rats: a pilot study

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ABSTRACT

Purpose: The influences of radiofrequency electromagnetic exposure on animal health, particularly on serotonin metabolism, are not well-elucidated. In this in vivo study, we studied the influences of exposure to radiofrequency identification (RFID) signals on serotonin metabolism.

Materials and methods: Twenty-two male Sprague–Dawley rats were assigned to sham ($n = 10$) and RFID-exposed ($n = 12$) groups. Rats in the RFID-exposed group were exposed to RFID signals at an average whole-body specific absorption rate of 2 W/kg for 8 h/day, 5 days/week for 2 weeks. Before and after RFID exposure, 24-h urine was collected from each rat. Urinary tryptophan, 5-hydroxytryptophan, serotonin, 5-hydroxyindoleacetic acid, and 5-methoxyindole-3-acetic acid concentrations were examined using gas chromatography-mass spectrometry, and changes in the patterns of values were compared between the two groups.

Results: Urinary levels of serotonin decreased by 20% ($p = .041$, Student's t-test) and 40% ($p = .024$, Student's t-test) in both the sham and RFID-exposed groups, respectively. The level of 5-methoxyindole-3-acetic acid decreased by 30% in the RFID-exposed group ($p = .039$, Student's t-test).

Conclusion: Our results indicate that exposure to RFID signals at a specific absorption rate of 2 W/kg is sufficient to alter serotonin metabolism in rats regardless of whether the exposure level is considered biohazardous.

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Introduction

Recently, mobile telecommunication systems have been widely used. In 2020, more than 4.7 billion people are using mobile phones globally, and the number is continuously increasing. As wireless networks, including wireless local area networks, relay information using radiofrequency (RF) signals, the public is exposed to continuous low-level RF electromagnetic fields (RF-EMF), although the change of body temperature was not statistically significant at this exposure level. In addition, humans may be absorbing invisible RF energy through the entire body due to the ubiquitously installed wireless networks that we are exposed to in daily life. Accordingly, the general public is concerned about potential health influences from exposure to RF-EMF via mobile communication technology.

Serotonin (5-hydroxytryptamine) is a monoamine neurotransmitter also known as a 'happy chemical' that can modulate various neurological mechanisms such as mood, sleep, circadian rhythm, learning, memory, and stress (Berger et al. 2009; Weng et al. 2015). Serotonin deficiency is observed in a broad range of diseases, including various neurodegenerative diseases and depression (Berger et al. 2009; Weng et al. 2015). One of the main metabolites of serotonin is 5-hydroxyindoleacetic acid (5-HIAA), the urinary concentration of which is an index of turnover of its parent neurotransmitters in the central nervous system (Sullivan et al. 2006). Changes in serotonin turnover caused by various environmental stressors can lead to decreased urinary levels of 5-HIAA (Tarantino et al. 2011). Urinary levels of 5-HIAA are used for diagnosing intestinal neuroendocrine tumors, and high levels indicate the need for follow-up (Tarantino et al. 2011).

In mammals, roughly 95% of serotonin is synthesized in the gastrointestinal tract (Terry and Margolis 2017), and the rest is produced in the central nervous system. Tryptophan (TRP), a serotonin precursor, is converted into 5-hydroxytryptophan (5-HTP) by TRP hydroxylase. Subsequently, 5-HTP is converted into serotonin by aromatic-L-amino-acid

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decarboxylase (Agus et al. 2018; Dehhaghi et al. 2019). Serotonin is widely distributed to several target organs and is broken down by monoamine oxidase to produce 5-HIAA (O'Mahony et al. 2015). Finally, 5-HIAA is converted into 5-methoxylindole-3-acetic acid (5-MIAA) by hydroxylindole-*O*-methyltransferase and excreted by the kidneys (Ho et al. 2001). These cascades are shown in both the central nervous system and the enteric nervous system. Serotonin is a crucial neurotransmitter in the brain–gut axis (Jenkins et al. 2016) and plays a wide-ranging regulatory role in the physiology of the whole body, including the immune system (Wu et al. 2019). However, few animal studies have reported the influences of RF-EMF exposure on serotonin metabolism, and the results reported to date have been inconsistent (Snyder 1971; Catravas et al. 1976; Maaroufi et al. 2014; Li et al. 2015). In one report, levels of serotonin and 5-HIAA in the brain increased following continuous exposure to 3000-MHz RF signals at a specific absorption rate (SAR) of 8 W/kg for 1 h. By contrast, serotonin and 5-HIAA levels decreased following exposure to the same RF signals at a SAR of 2 W/kg for 8 h/day for 7 days (Snyder 1971). In another animal study, serotonin concentrations and TRP hydroxylase activity in the diencephalon increased after exposure to 10 mW/cm^2 of RF signals for 8 h/day (Catravas et al. 1976).

The influences of exposure to RF on serotonin metabolism remain unknown, as the available information on this topic is limited. Therefore, we conducted an animal study to evaluate the influences of exposure to RF signal on serotonin in rats.

Materials and methods

Whole-body radio frequency identification exposure system

A reverberation chamber with a 915 MHz radio frequency identification (RFID) signal source (Jung et al. 2008) was constructed to assess whole-body exposure (IRETEC, Anyang, Korea) as described in a previous study (Kim et al. 2018). In brief, field distribution was measured directly, and field uniformity was confirmed in the reverberation chamber using a three-axis isotropic probe (HI-6105; ETS-Lindgren, Cedar Park, TX). The average whole-body SAR in the American Air Force Research Lab [AFRL] rat model (Dayton, OH) was calculated for the measured electric field strength using a commercial finite-difference time-domain tool (XFDTD version 6.5; Remcom, State College, PA, USA) for incident plane waves in six orthogonal directions with two polarizations. To calculate the change in SARs, we used a scaled rat model modified from the adult AFRL rat model, which estimated 36 tissues assuming a mass of 339 g and with a voxel size of $0.39 \times 0.39 \times 0.42$ mm^3. The output power level was managed by an 11-bit digital personal identification number diode attenuator (Model 349; General Microwave, Farmingdale, NY). The input power was set to 34 W on the basis of the SAR calculations, which led to an average whole-body SAR of 2 W/kg in the rat model.

Animal experiments

In total, 22 male Sprague–Dawley rats (6 weeks old, weight 200–250 g; Dae-Han Biolink, Seoul, Republic of Korea) were used in the current study. Rats were maintained at a temperature of 22 ± 2 °C and housed under a 12/12-h light/dark cycle with water and food (Dae-Han Biolink) *ad libitum*. Animals were randomly divided into two groups: the sham ($n = 10$) and RFID-exposed ($n = 12$) groups. Rats in the sham group were placed in the RF exposure system of the reverberation chamber but not exposed to RFID signals. Rats in the RFID-exposed group were placed in the RF exposure system and exposed to RFID signals at a whole-body SAR of 2 W/kg for 8 h/day, 5 days/week for 2 weeks. Access to food and water was disallowed during the exposure period in the sham and RFID-exposed groups.

Urine sample collection

For each rat, 24-h urine was collected twice, on the day before the beginning of the 2-week RFID exposure trial, and after the end of the trial (Paik et al. 2016). The total volume of each 24-h urine sample was measured. The collected 24-h urine was centrifuged (3000 × *g*, 20 min) to eliminate debris and preserved at −70 °C until processing. All experiments were performed in accordance with the approval of the Ethics Committee of Animal Experiments (110405–25) of Ajou University School of Medicine (Suwon, Korea).

Sample preparation for serotonin analyses using gas chromatography-selected-ion monitoring-mass spectrometry (GC-SIM-MS)

Serotonin in each urine sample was analyzed using ethoxycarbonyl (EOC)-pentafluoropropionyl (PFP) derivatives (Paik et al. 2010). Briefly, 0.5 mL of each urine sample and 0.5 mL of distilled water containing 0.1 μg 1,6-diaminohexan as an internal standard was added to 1.0 mL dichloromethane containing 20 μL of ethyl chloroformate, and the pH of the solution was adjusted to ≥12 with 5.0 M NaOH. Then a two-phase EOC reaction was performed with swirl mix for 10 min, the pH was adjusted to ≤2 with 10% H_2SO_4, and the solution was saturated with NaCl. Next, reaction mixtures were sequentially extracted with 3 mL of diethyl ether and 2 mL of ethyl acetate. The combined extracts were evaporated under a gentle stream of nitrogen and subjected to PFP derivatization by reacting them for 30 min at 60 °C with 20 μL of PFP anhydride for GC-SIM-MS analyses.

Sample preparation for analyzing 5-HIAA, 5-MIAA, TRP, and 5-HTP via GC-SIM-MS

Simultaneous profiling analyses of 5-HIAA, 5-MIAA, TRP, and 5-HTP were attempted using EOC/*tert*-butyldimethylsilyl derivatives (Paik et al. 2008). Briefly, 0.5 mL of each urine sample and 0.5 mL of distilled water containing norvalin and 0.1 μg 3,4-dimethoxybenzoic acid as internal

standards were added to 1.0 mL of dichloromethane containing 20 μL of ethyl chloroformate, and the pH of the solution was adjusted to ≥12 with 5.0 M NaOH. Then a two-phase EOC reaction was carried out with swirl mix for 10 min, the pH was adjusted to ≤2 with 10% H_2SO_4, and the solution was saturated with NaCl. Next, reaction mixtures were sequentially extracted with 3 mL of diethyl ether and 2 mL of ethyl acetate. The extracts were evaporated to dryness under a gentle stream of nitrogen. Dry residues containing 5-HIAA, 5-MIAA, TRP, and 5-HTP were reacted at 60 °C for 30 min with 5 μL of trimethylamine, 20 μL of toluene, and 20 μL of N-(*tert*-butyldimethylsilyl)-N-methyltrifluoroacetamide to form *tert*-butyldimethylsilyl derivatives.

Star plots

Levels of TRP, 5-HTP, serotonin, 5-HIAA, and 5-MIAA were normalized using the corresponding before-exposure group mean, and then each normalized value was plotted along a line radiating from a common central point. The far ends of the lines were connected to generate star patterns using Microsoft Excel (Microsoft, Redmond, WA) (Paik et al. 2016).

Statistical analyses

All data were presented as means ± standard deviations. Statistical analysis was performed using Student's *t*-test with SPSS ver. 12.00 for Windows (SPSS, Chicago, IL, USA). A *p*-value < .05 was considered to denote statistical significance.

Results

Influences of RFID exposure on profiles of serotonin metabolites in rat urine

Levels of serotonin in the sham-exposed group before and after exposure were 54.64 ± 11.66 and 40.99 ± 15.66 (nmol/mg of creatinine), respectively ($n = 10$, $p = .041$, Student's *t*-test, Table 1). Levels of serotonin in the RFID-exposed group before and after exposure were 50.89 ± 22.38 and 29.96 ± 14.89 (nmol/mg of creatinine), respectively ($n = 12$, $p = .024$, Student's *t*-test, Table 1). The change in serotonin levels was larger in the RFID-exposed group than in the sham-exposed group. Levels of 5-MIAA in the RFID-exposed group before and after exposure were 6.28 ± 1.80 and 4.39 ± 2.00 (nmol/mg of creatinine), respectively ($n = 12$, $p = .039$, Student's *t*-test, Table 1). No statistically significant change in 5-MIAA level was observed in the sham-exposed group after exposure ($p > .05$). No statistically significant changes in TRP or 5-OH-TRP levels were observed in either group after exposure ($p > .05$).

Star plots

The mean and normalized levels of the serotonin metabolites as well as changes in the levels of serotonin metabolites before and after exposure (Paik et al. 2016) are summarized in Table 1. Normalized levels of serotonin metabolites were plotted as response variables in star plots consisted of five rays to visualize the differences in serotonin metabolites between the two groups (Figure 1). A contorted star pattern was observed for each group after exposure. In the sham group, 5-HIAA and 5-HTP levels increased after exposure, but these differences were not statistically significant. In the RFID-exposed group, 5-HIAA and 5-HTP levels decreased after exposure, but the differences were also not statistically significant. After exposure, TRP levels increased in the RFID-exposed group and decreased in the sham-exposed group, but the differences were not statistically significant.

Discussion

The biological influences of RF exposure on serotonin metabolism are not well elucidated. In this animal study, we found that exposure to RFID signals led to by 40% and 30% decreases in concentrations of serotonin and 5-MIAA in rat urine, respectively.

In an animal study, pregnant female rats were radiated to cellphone signal at a rate of 15 missed calls/day during 21 days of pregnancy, and infant rats were exposed to the same condition. Serotonin levels in the pups were measured on days 1, 7, 14, 21, and 28 after delivery, and statistically significant increases in serotonin levels were shown in the brain after RF exposure. In another rat study, animals were radiated to a 900 MHz global system for mobile communication (GSM) EMF for 1 h/day for 21 days at a SAR ranging from a minimum of 0.05 W/kg to a maximum of 0.18 W/kg

Table 1. Levels of serotonin metabolites in rat urine (nmol/mg creatinine) before and after sham and RFID exposure.

	Mean ± SD				Normalized value[a]					
	Sham ($n = 10$)		RFID ($n = 12$)		Sham ($n = 10$)		RFID ($n = 12$)		*p*-Value[b]	
Analytes	Before	After	Before	After	Before	After	Before	After	Sham	RFID
5-HIAA	97.89 ± 77.50	144.19 ± 122.78	169.29 ± 82.78	105.89 ± 50.13	1.0	1.5	1.0	0.6	.327	.053
5-MIAA	7.75 ± 2.46	6.15 ± 2.18	6.28 ± 1.80	4.39 ± 2.00	1.0	0.8	1.0	0.7	.141	.039
Serotonin	54.61 ± 11.66	40.99 ± 15.66	50.89 ± 22.38	29.96 ± 14.89	1.0	0.8	1.0	0.6	.041	.024
Tryptophan	89.26 ± 47.03	81.44 ± 28.91	97.54 ± 68.23	112.74 ± 36.59	1.0	0.9	1.0	1.2	.660	.543
5-HTP	33.20 ± 24.24	50.04 ± 30.39	57.99 ± 35.59	47.21 ± 22.26	1.0	1.5	1.0	0.8	.188	.427

The data are expressed as mean ± standard deviation (SD).
SD: standard deviation; Sham: sham-exposed group; RFID: radiofrequency-exposed group; 5-HIAA: 5-hydroxyindoleacetic acid; 5-MIAA: 5-methoxylindole-3-acetic acid; 5-HTP: 5-hydroxytryptophan.
[a]Values normalized to the corresponding control mean value. [b]From Student's *t*-tests comparing values before and after exposure.
*Statistically significant at $p < .05$.

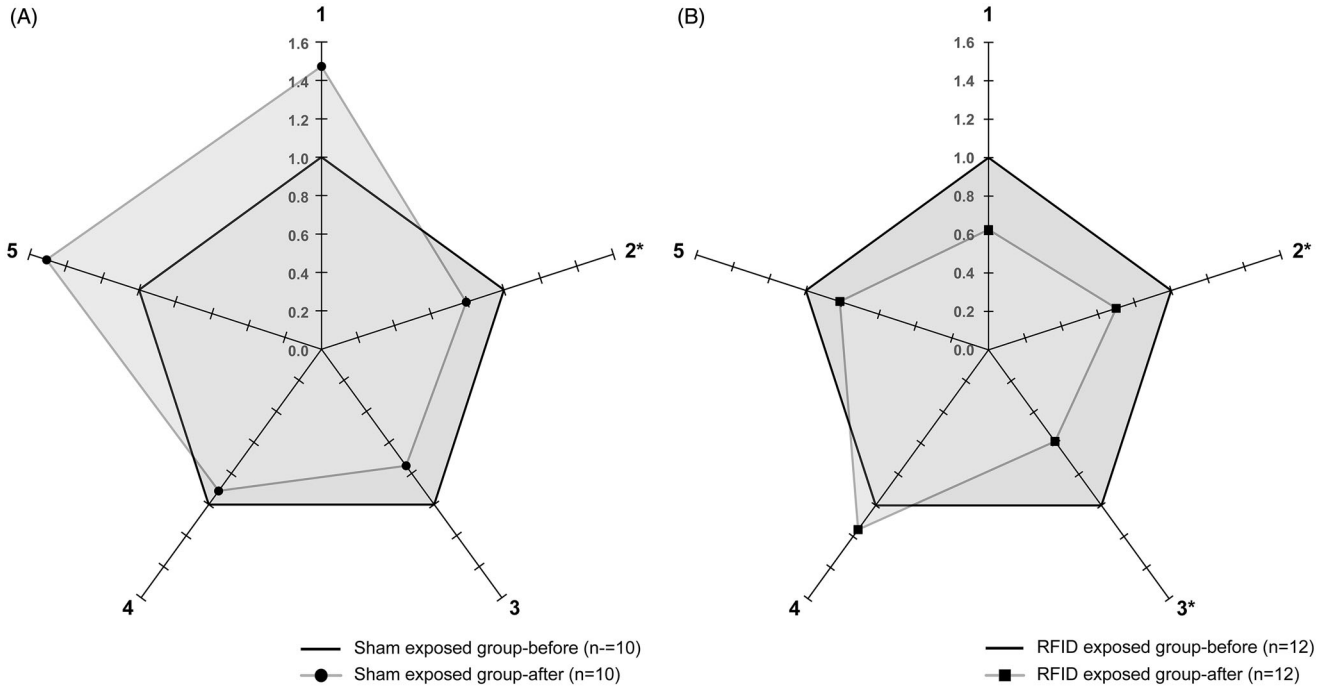


Figure 1. Star plots of mean normalized levels of serotonin metabolites for the (A) sham and (B) radiofrequency identification signal (RFID)-exposed groups before and after the exposure trials. Levels were normalized based on the corresponding mean value before exposure. $^{*}p < .05$, Student's *t*-test. (1) 5-hydroxyindoleacetic acid (5-HIAA); (2) 5-methoxylindole-3-acetic acid (5-MIAA); (3) Serotonin; (4) Tryptophan; (5) 5-hydroxytryptophan (5-HTP).

corresponding to the rat's positions (Maaroufi et al. 2014). Serotonin levels increased in the cerebellum and decreased in the hippocampus following exposure to 900 MHz EMF. The rats also performed more poorly in object-exploration tasks after RF-EMF exposure, implying that radiation to 900 MHz signal disrupted the general memory process. However, a clear relationship between changes in serotonin levels and a memory deficit was not observed. (Li et al. 2015) observed an increment in serotonin and a decrement in 5-HIAA in the rat hippocampus when subjects were radiated to 2.856 GHz microwave signal at rates of 5, 10, 20, and 30 mW/cm^2 for 6 min three times a week for up to 6 weeks. Their findings imply that chronic microwave exposure can disrupt serotonin metabolism, resulting in cognitive deficits. Although the influence of RF exposure on serotonin metabolism has been studied in a few reports, the results of the studies are controversial because the methods used for RF-EMF exposure have been inconsistent. Still, exposure to RF-EMF does lead to changes in serotonin metabolism and likely influences disease occurrence. For example, in one study, spatial learning and memory in the rat were impaired following exposure to 2.45 GHz pulsed microwave at a power density of 1 mW/cm^2 for 3 h/day for 30 days (Lu et al. 2012). Statistically significant memory deficits have also been observed in rats after exposure to 900 MHz GSM cellphone signal at average whole-body SARs of 0.6 and 60 mW/kg for 2 h/week for 55 weeks (Nittby et al. 2008). Although the influences of RF exposure on serotonin metabolism were not analyzed in these studies, changes in serotonin metabolism induced by RF exposure could be a possible cause of cognitive defects.

In the present study, we measured urinary levels of serotonin metabolites to evaluate the TRP metabolic pathway. The levels of TRP and 5-HTP remained unchanged after RF exposure, whereas serotonin and 5-MIAA levels decreased. The serotonin/5-HIAA ratio did not change after exposure in either group (data not shown). Given the limited results obtained in this study, we do not have enough evidence to discuss the mechanism underlying changes in serotonin synthesis. However, our results imply that exposure to RF-EMF influences the serotonin synthesis pathway rather than serotonin turnover. In mammals, the kynurenic pathway is a major component of the TRP metabolic pathway. By contrast, the serotonin pathway is a minor component. TRP is transformed via the kynurenic pathway into bioactive compounds that can possibly affect stress responses (Le Floc'h et al. 2011). Furthermore, stress can cause the TRP metabolic pathway to shift from serotonin production toward the kynurenic pathway (O'Farrell and Harkin 2017). However, the influences of RF exposure on the kynurenic pathway were not evaluated in the present study. Previous studies have shown that RF exposure, as a stressor in animals, can induce stress responses including the production of heat shock proteins (Lixia et al. 2006) and stress hormones (Shahabi et al. 2018). Therefore, we suspect that RFID exposure decreases serotonin synthesis by diverting available TRP to the kynurenine pathway.

This study had some limitations. This study was not comprehensive due to a single study using a few animals at a single exposure condition. Although marked alterations in the levels of serotonin and 5-MIAA were observed, additional animal studies applying different levels of RF exposure may be needed as a whole-body SAR of 2 W/kg for 2 weeks may not be sufficient to produce long-term influences in rats. It would also be useful to study the RF dose-response relationship with lower SARs. Therefore, further

study is needed to assess the influences of chronic RF exposure on the serotonin metabolic pathway and elucidate the mechanism underlying changes in serotonin metabolism due to RF exposure. As aging is a risk factor for neuropsychiatric disorders related to serotonin dysfunction, future studies should also include aged animals as subjects. Serotonin turnover increases in patients with depressive disorder, with brain concentrations of 5-HIAA decreasing in patients with depression (Barton et al. 2008). However, the brain provides less than 10% of the 5-HIAA found in urine and plasma (Barton et al. 2008). In this study, we measured serotonin metabolites in rat urine, but urinary levels of 5-HIAA may not reflect changes in serotonin turnover. Thus, further studies are needed to analyze serotonin metabolites in the cerebrospinal fluid and pineal gland.

Conclusions

Exposure to RFID signals, at least under experimental conditions, may alter serotonin synthesis in rats, regardless of whether the exposure level is biohazardous. Further research to assess the influences of RFID exposure on serotonin synthesis and elucidate details of the mechanism underlying such changes is needed.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Notes on contributors

Hye Sun Kim has a PhD degree in neuroscience and planned and performed the animal experiments.

Man-Jeong Paik has a PhD degree in pharmacy and contributed to the metabolomics analyses.

Chan Seo has a PhD degree in pharmacy and contributed to the metabolomics analyses.

Hyung Do Choi has a PhD degree in material engineering and calculated the EMF strengths and SARs.

Jeong-Ki Pack supervised the construction of the RF chamber.

Nam Kim supervised the construction of the RF chamber.

Young Hwan Ahn is a neurosurgeon with a PhD degree in medicine and directed and planned this study.

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