Chapter 14
The Biological Effects of Long-Term Static Magnetic Field Exposure

Hanxiao Chen and Xin Zhang

Abstract Although in most cases, people are exposed to static magnetic fields (SMFs) for just a short period of time, there are increasing situations where long-term exposure becomes inevitable, including magnets implanted in patients, magnetic therapy, and occupational exposure of magnetic resonance imaging staff. Consequently, the potential beneficial and/or harmful effects of such exposure, as well as its underlying mechanism, have triggered research endeavors. In this chapter, we have collected reported experimental data on animals and humans that were subjected to SMFs for more than 2 weeks, either continuously or intermittently. In animal models, it is found that long-term exposure to moderate SMFs can influence multiple aspects, including blood pressure and glucose regulation, the relief of pain, the promotion of bone formation, etc. Differences between continuous vs. intermittent exposure, human experimental results vs. epidemiological studies are discussed. Although most animal and human studies so far have suggested little/no risk of long-term exposure, or even beneficial effects for most moderate SMFs, there are still some exclusions that need attention. More research is still needed to comprehensively assess the exact long-term biological effects of various SMFs on different physiological and pathological conditions before we can make the best use of them.

Keywords Static magnetic fields (SMFs) · Long-term exposure · Biological effects · Continuous and intermittent exposure · Implanted and non-implanted magnets

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14.1 Introduction

Magnetic fields can be divided into different types depending on their parameters. A constant magnetic field, which does not change in magnetic flux density or direction over a certain period of time, is called static magnetic field (SMF). For example, the earth is surrounded by quasi-SMFs of 25 μT (tesla) and 65 μT, which are static for a certain period of time, but can also be affected by solar wind. Aside from this, there are many applications of SMFs such as the core part of magnetic resonance imaging (MRI) machines, the nuclear magnetic resonance (NMR) spectrometer, and the MagLev trains. Due to the increased exposure to SMFs in the last few decades, the interaction between SMF and organisms has become a rapidly developing research area.

Up to now, researchers have identified several biophysical mechanisms of SMF in organisms, including electrodynamic interactions with ionic conduction currents, the orientation of magnetically anisotropic structures in uniform fields, the translational force exerted on a paramagnetic or ferromagnetic substance placed in a magnetic field gradient, and modification of chemical reactions (Maret and Dransfeld 1977; World Health Organization 2006; Torbati et al. 2022). Although the theories are relatively straightforward, due to the complexity of the biological systems and the variability of magnetic fields in independent studies, the interpretations of the various experimental observations have been very complicated and inconsistent, which was discussed in Chap. 1 of this book.

Currently, there are largely two groups of people that could have long-term and/or repeated SMF exposures. One group includes workers in MRI examinations in hospitals, as well as in magnet factories, who are occupationally exposed to magnetic fields. The other group includes people who use magnetic fields to alleviate disease symptoms or improve health. For example, a magnet can be implanted on the sternum and is paired with an external magnetic brace to treat patients with pectus excavatum (Jamshidi and Harrison 2007) or implanted around the distal esophagus in patients with gastroesophageal reflux disease (GERD) (Bortolotti 2021) (Fig. 14.1), both of which fall in the category of magnetic surgery. There are also many people who use SMF-based magnetic mattress and bracelet, etc. Therefore, it is important to find out the exact long-term biological effects of magnetic fields and their potential actions on human bodies.

Here we have collected recent studies of long-term SMF exposure (over a period of 2 weeks or longer, continuously or intermittently) in animals and humans, with a special focus on the detailed magnetic field parameters, which has been proved to be very critical in the previous chapters of this book. We analyze their results in the hope of providing better understandings of the long-term biological effects of SMF on living organisms so that we can take the best advantage of them in the future.

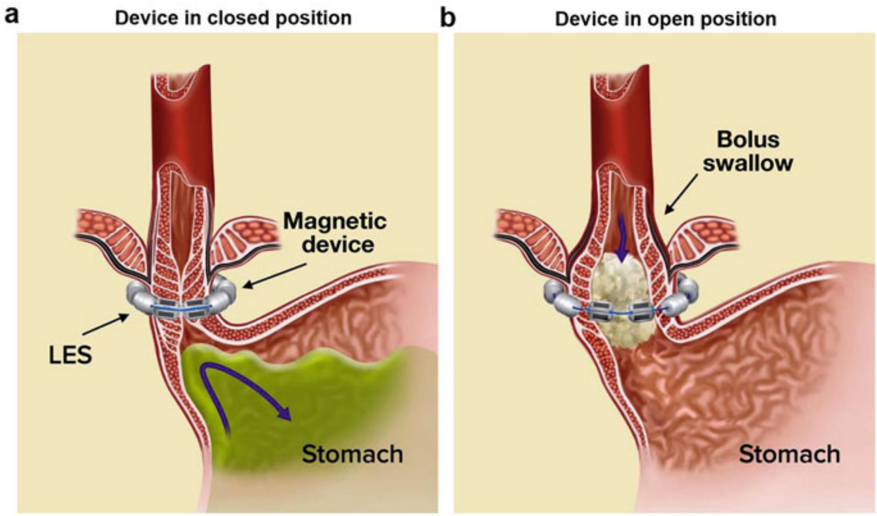

Fig. 14.1 Magnetic sphincter augmentation device that has been used on human bodies for years. (LINX Reflux Management System, Torax Medical, Shoreview, MN, USA) (**a**) Device in closed position; (**b**) device in open position. [Reprinted with permission from (Ganz et al. 2016). Copyright © 2015 The AGA Institute]

14.2 Animal Studies

In this review, we screened studies that were exposed to SMFs for longer than 2 weeks, which are further classified into continuous (SMF exposure 24 h/day for over 2 weeks) and intermittent (SMF exposure for several minutes or hours a day for over 2 weeks) exposure. Most relevant animal studies used rodents, while other animal models, such as zebrafish, medaka fish, and marine benthic animals, were also used.

14.2.1 Continuous Exposure

In this type of experiment, animals are exposed to SMFs 24 h/day for more than 2 weeks, either non-implanted or implanted.

14.2.1.1 Non-implanted

Non-implanted refers to the situations that the magnetic devices were not placed into the animal or human bodies. The magnetic devices, either permanent magnets or electromagnets, are placed outside of the animal or human bodies so that the SMF

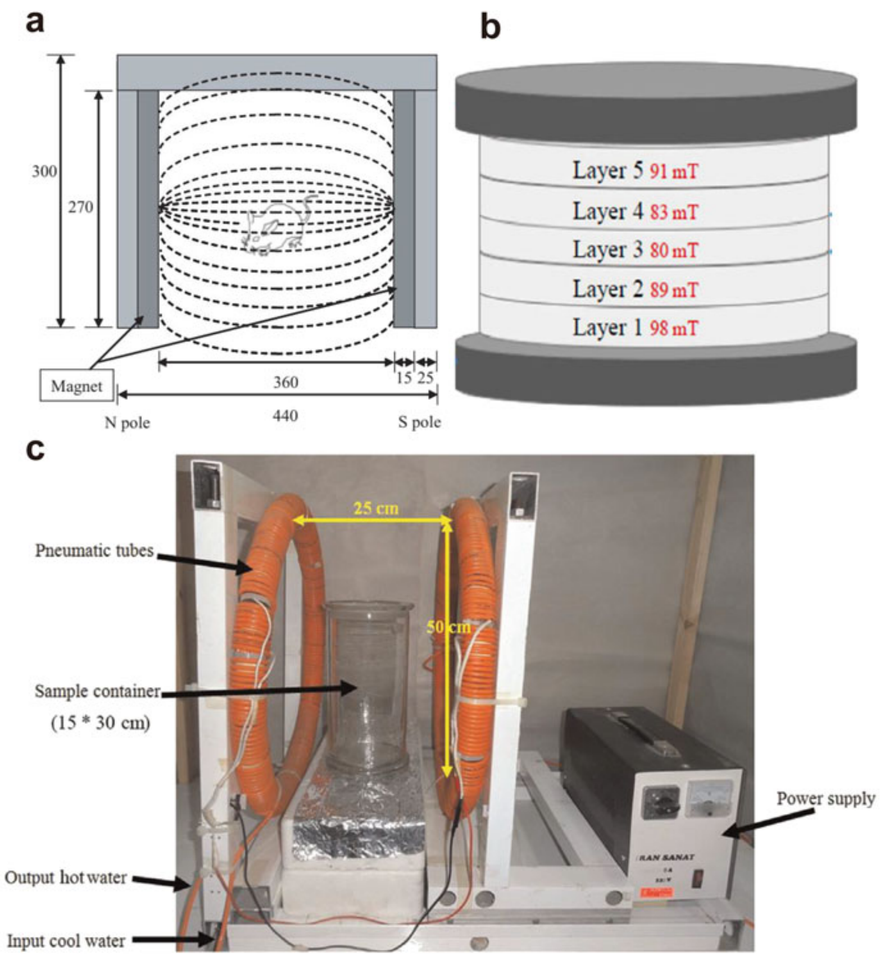

Fig. 14.2 Examples of SMF exposure set-ups for non-implanted SMF studies. Two permanent magnets were placed on opposite sides of (**a**) the mice cage (Taniguchi and Kanai 2007). Copyright © 2006 The Authors (open access); and (**b**) dishes with the fish embryos (Sun et al. 2019). Copyright © 2019 The Authors (open access); (**c**) device used to produce electromagnetic fields. [Reprinted with permission from (Loghmannia et al. 2015). Copyright © 2014 Elsevier Inc.]

can penetrate the whole body or the specific target area (Fig. 14.2). This is actually the most common way to perform magnetobiology studies. The results of continuous long-term SMF exposure by non-implanted magnet on animals are summarized, including the influence on reproductive system, blood pressure, pain relief, etc. (Table 14.1).

From Table 14.1, we can see that there are multiple studies about the reproductive system. In fact, there has always been a concern about the influence of environmental conditions on the reproductive system because it is much more sensitive and

Table 14.1 Continuous long-term SMF exposure (non-implanted) on animals

Subjects	Magnet type	Flux density	Time	Effects	Classification	References
Mussels M. edulis	Electromagnet	0.0037 T	3 months	No changes in gonad index and condition index	Reproductive system	Bochert and Zettler (2004)
Medaka fish	Permanent magnet	~0.1 T	15 days	No impacts on embryo development		Sun et al. (2019)
Albino mice		0.5–0.7 T	Gestation to birth	No changes in the body or testis-epididymis weight gain of pups		Tablado et al. (2000)
Albino mice		0.7 T	35 days	No changes in testicular or epididymal weights		Tablado et al. (1996)
				No changes in sperm head size but increase sperm head abnormality		Tablado et al. (1998)
Spontaneously hypertensive rats		0.005 T	12 weeks	Suppress and delay blood pressure elevation	Blood pressure regulation	Okano et al. (2005a)
Wistar-Kyoto rats		0.025 T		Reverse the reserpine-induced symptoms of reduced blood pressure		Okano et al. (2005b)
Spontaneously hypertensive rats		0.01 T, 0.025 T		Suppress and retard the development of hypertension		Okano and Ohkubo (2003)
Wistar rats		0.012 T	10 weeks	Depress sympathetic agonists-induced hypertension and hemodynamics changes		Okano and Ohkubo (2007)
Spontaneously hypertensive rats		0.016 T	30 days	Reduce arterial blood pressure, enhance baroreceptor reflex sensitivity		Tasić et al. (2017)
Sprague-Dawley rats		0.03 T (range 0.02–0.08 T)	12 weeks	The pain relief effects increased with activity and BMD	Pain relief	Taniguchi et al. (2004)
			4 weeks	Improve blood flow and reactive speed response, relief pain		Kanai and Taniguchi (2012)
Wistar rats			12 weeks	Inhibit the reduction in bone mineral density	Skeleton system	Taniguchi and Kanai (2007)

(continued)

Table 14.1 (continued)

Subjects	Magnet type	Flux density	Time	Effects	Classification	References
C57BL/6J mice		0.6 T	21 days	Reduce all-trans retinoic acid-induced bone loss		Chen et al. (2020)
			3 months	Reduce dexamethasone-stimulated osteoporosis		
Wistar albino rats		0.001 T	50 days	Increase ATPases, AChE activities, and MDA level	Synaptosomes	Dinčić et al. (2018)
BKS-Lepr^{db}/J mice		0.015 T	10 weeks	Promote the diabetic wound healing process	Diabetic complications	Feng et al. (2022)
C57BL/6J mice		0.1 T	12 weeks	Prevent high blood glucose, weight gain, fatty liver		Yu et al. (2021)
Sprague-Dawley rats		0.18 T	19 days	Promote the diabetic wound healing process and strengthen the wound tensile strength		Jing et al. (2010)
C57BL/6 mice	Superconducting magnet	2–12 T	28 days	No differences in physiological indexes	A safety study	Wang et al. (2019)

vulnerable to external stimuli compared with other systems. A research about marine benthic animals demonstrated that when *Mussels M. edulis* was kept in a 3.7 mT SMF for 3 months during their reproductive period in spring, the gonad index and condition index revealed no significant differences from the control group (Bochert and Zettler 2004). The embryo development in medaka fish in vivo with long-term SMF exposure did not reveal any impact on embryo development with 15-day exposure of up to ~100 mT (Sun et al. 2019). Tablado et al. exposed mice to a 0.7 T SMF for 35 days, and no changes were observed in their testicular or epididymal weights, and the size of sperm heads was also unaffected (Tablado et al. 1996, 1998). However, an increase in percentage of sperm head abnormality (lack of hook) was observed (Tablado et al. 1998). Tablado et al. also showed that the exposure of pregnant mice to a 0.5–0.7 T SMF did not change the body or testis-epididymis weight gain in pups (Tablado et al. 2000). Although not much abnormalities have been reported in this aspect, since the number of relevant studies is too limited, we still need more investigations to make sure the exact influence of long-term SMF exposure on reproductive system. We have also published a review about the SMF effect on reproductive system, including various exposure conditions (Song et al. 2022).

There are also several studies that have explored the effects of SMFs in blood pressure regulation. In 2003, Okano et al. found that 3.0–10.0 mT or 8.0–25.0 mT SMF exposure for 12 weeks can suppress and retard the development of hypertension in spontaneously hypertensive rats (Okano and Ohkubo 2003). In addition, lower field of 5 mT produced the same effect of reducing blood pressure but 1 mT did not have such effect (Okano et al. 2005a). This conclusion was confirmed in 2017 by Tasić et al. (2017). Besides, it was shown that a loop-shaped flexible rubber magnet adjusted to the neck region of a rat with intraperitoneal phenylephrine and dobutamine for 10 weeks can significantly depressed agonist-induced hypertension (Okano and Ohkubo 2007). However, it is interesting that Okano et al. have compared the effect of a 25 mT SMF on normotensive (having normal blood pressure) vs. hypotensive rats. They found that the 25 mT SMF did not cause any cardiovascular changes during an exposure period of 3 months (Okano et al. 2005b) but can significantly inhibit the reserpine-induced hypotension (Okano et al. 2005b). These indicate that SMFs may not affect normotensive animals, but could affect blood pressure in pathological conditions. It is very interesting and also puzzling that SMFs seem to be able to “properly” regulate blood pressure in these animals, by raising or lowering blood pressure to bring it back to the normal level. However, it should be mentioned that many of these studies were performed by the same group of researchers. Therefore, more research is needed to unravel these intriguing regulation effects of SMFs on blood pressure regulation.

Other aspects of SMF influences were also investigated, including pain relief, skeleton system, wound healing, and other diabetic complications. For example, adjuvant arthritis rats exposed to 30 mT SMF for 12 weeks not only had a pain relief effect, but also increased bone mineral density (BMD) (Taniguchi et al. 2004). Using the same experiment conditions, Taniguchi et al. found that the ovariectomized (OVX)-induced BMD reduction could also be inhibited by SMF treatment, indicating its potential to be used to reduce menopausal symptoms in postmenopausal women (Taniguchi and Kanai 2007). Chen et al. proposed that the magnetic fields influence bone formation by affecting the differentiation of bone marrow mesenchymal stem cells (Chen et al. 2020). And the pain relief is probably due to the improvement of blood flow induced by SMF (Kanai and Taniguchi 2012). The chronic SMF exposure can also increase ATPases, AChE (acetylcholinesterase) activities, and MDA (malondialdehyde) level in rat synaptosomes (Dinčić et al. 2018). Moreover, it has also been shown that the long-term SMF treatment can have positive effects on diabetic wound healing and other diabetic complications (Jing et al. 2010; Yu et al. 2021; Feng et al. 2022).

It should be pointed out that most long-term SMF exposure studies have used SMFs of <1 T, which is mainly because of experimental setup limitations. However, there is one study that has addressed the biological effects of high SMF (2–12 T) exposure on mice continuously for 28 days. They used a large bore, superconducting magnet to perform this study. The results showed that there were no differences in the body weight, organ coefficients, or histomorphology of major organs in mice after exposure (Wang et al. 2019), which provides essential biosafety information for the future development of high-field SMFs in medicine.

14.2.1.2 Implanted

With the development of magnetic surgery technology, long-term magnet implantation has been shown to be useful in treating multiple diseases, such as pectus excavatum (Jamshidi and Harrison 2007; Bortolotti 2021), gastroesophageal reflux disease (Bortolotti 2021), etc. Moreover, numerous studies have reported the positive effects of moderate SMF on bone system, immune system, and the nervous system, which has been discussed in Chaps. 11, 12, and 13 of this book. It is therefore necessary to explore the safety and biological effects of long-term magnet implantation so that we can take the best advantage of the SMF in medicine in the future.

There are multiple studies using implanted magnets to examine their effects on skeleton system (Table 14.2). In 1998, Yan et al. implanted tapered rods with magnetization in bilateral femurs of rats and measured their BMD and bone calcium content 12 weeks after implantation, which revealed that the values increased compared with unmagnetized group (Yan et al. 1998). The same SMF intensity but with a treatment time of 21 days also leads to an improved osteogenesis (Nagai et al. 2000). A small disc magnet (max. 180 mT) implanted to OVX rats for 6 weeks statistically significantly increased BMD value and improved clinical effect on osteoporotic lumbar vertebrae (Xu et al. 2011) (Fig. 14.3). Some researchers think that the improved collateral circulation and blood circulation are the root cause of promoting bone formation. Ischemic rats whose femoral artery was ligated had reduced BMD and weight, and these can be reversed at the third week post-implantation of 180 mT magnets (Xu et al. 2001).

Table 14.2 Continuous long-term SMF exposure (implanted permanent magnets) on animals

Subjects	SMF flux density	Period of time	Effects	Classification	References
Wistar rats	0.01–0.017 T	7 days	Increase width of the periodontal ligament and root resorption	Orthodontic tooth movement	Tengku et al. (2000)
		14 days	No differences in tooth movement		
	0.06 T	14 days	Increase the number of CD4+ lymphocytes	Immune response	Janković et al. (1991)
		24 days	Increase the size of the thymus, hemagglutinin titer, and the number of CD4+ lymphocytes		
		34 days			
		25 days	Increase the number of plaque-forming cells and hemag-glutinin titer in normal and pinealectomized rats, the former is more obvious		Janković et al. (1993b)
Rats		21 days	Potentiate immune responses in normal rats, and abrogate the immunosuppression induced by destruction of the locus ceruleus		Janković et al. (1993a)
Wistar rats	0.16 T	3–7 weeks	Increase vasomotion amplitude	Hemodynamics and vasoconstriction	Xu et al. (2013)
Spontaneously hypertensive rats	0.18 T	8 weeks	Increase nicardipine-induced hypotension		Okano and Ohkubo (2005)
		6 weeks	Enhance nicardipine-induced hypotension		Okano and Ohkubo (2006)
Wistar rats		12 weeks	Increase BMD and bone calcium content	Skeleton system	Yan et al. (1998)
		21 days	Improve osteogenesis in vivo		Nagai et al. (2000)
		6 weeks	Increase BMD value, clinical effect on osteoporotic lumbar vertebrae		Xu et al. (2011)
		3 weeks	Increase BMD and weight		Xu et al. (2001)
			Increase BMD and collateral circulation		Xu et al. (2007)

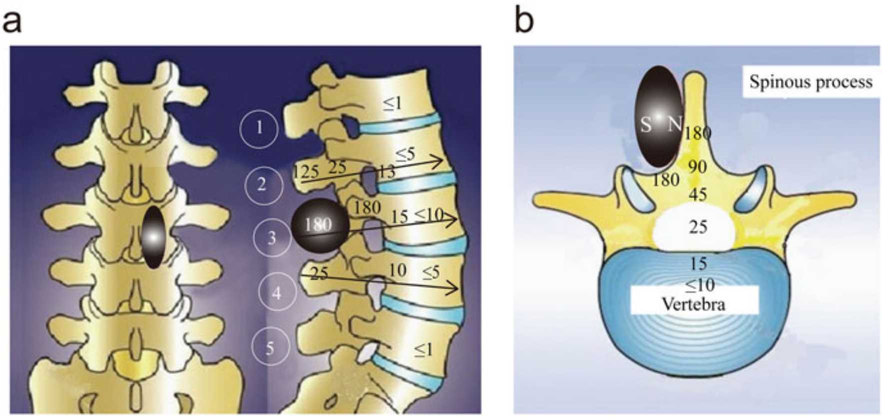

Fig. 14.3 Examples of SMF exposure with implanted magnets. Implanted magnet in lumbar vertebrae (**a**) and its spatial distribution (**b**). [Reprinted from (Xu et al. 2011), open access]

Studies have also indicated that SMFs can affect hemodynamics. In 2005, Okano et al. investigated the combined effects of a moderate SMF and nicardipine and found that the SMF induced a significant increase in the nicardipine-induced hypotension (Okano and Ohkubo 2005). Their subsequent research shows that the SMF may enhance nicardipine-induced hypotension by antagonizing the Ca^{2+} influx more effectively through the Ca^{2+} channels, or due to the upregulation of inducible nitric oxide (NO) synthase (Okano and Ohkubo 2006). Since blood vessel ingrowth is a pre-requisite for bone formation, a magnetized rod implantation for 3–7 weeks was shown to increase not only hemodynamics but also vasomotion (Xu et al. 2013). Therefore, although the studies are still very limited, these current results suggest that magnetic rod implantation may increase bone mineral density by altering hemodynamics, Ca^{2+} influx, and vasoconstriction. It is not clear why the permanent magnets in these studies, regardless of the rod or disk-like shape, all had a maximum magnetic field density of ~180 mT. We think it was probably the maximum flux density they can get at that time, being limited by the magnet size. More studies with different magnetic field conditions are encouraged for validation and/or improvement, which seems to be a promising future development for the application of SMFs, especially permanent magnets, in medicine.

There are also some researches about magnetic fields and immune response using implanted ways, which have been discussed in more details in Chap. 12 of this book. It should be mentioned that, theoretically, the movement of animals in SMFs can generate electrical currents leading to more bioeffects (Crozier et al. 2007). However, we did not find significant difference between the non-implanted and the implanted experiments, which may be due to the fact that SMF in most of these studies is not strong enough, and/or the animals are not actively moving.

14.2.2 Intermittent Exposure

Since intermittent SMF exposure over a period of time is more feasible in reality than continuous exposure, many studies have been carried out this way (Table 14.3). People have used different types of SMF devices in their research, including regular electromagnet and permanent magnet for lower SMF intensities, as well as superconducting and water-cooled magnets for higher SMF intensities.

The experiments with permanent magnets used magnetic flux densities of ~0.5 T. László et al. found that a max. 476 mT SMF is useful for chronic pain. They found a 30 min daily magnetic treatment for 2 weeks did not prevent the development of mechanical allodynia but can inhibit the increased sensitivity in neuropathic pain (Antal and László 2009). Besides, exposure for 6 weeks in the same experimental conditions significantly reduces plasma glucose level as compared to control in diabetic mice (László et al. 2010). They also demonstrated that daily 40-min whole body exposure to SMF prevented lipopolysaccharide (LPS)-induced preterm birth (PTB) in mice (László and Pórszász 2011). Tian et al. used permanent magnets with max. surface intensity of 0.5 T with upward direction, 6 h a day for 38 days, which inhibited GIST-T1 tumor growth in nude mice by 19.3% (Tian et al. 2018). No adverse effects were found in these studies.

For electromagnet-produced SMFs of varying strength, the effects are more diverse. It was shown that a 4 mT SMF exposure for 16 weeks (2 h/day) prevented bone architectural deterioration and strength reduction in type 1 diabetic rats (Zhang et al. 2018). And 2 h/day 5 mT SMF exposure for 14 days had no damage to noise-induced hearing loss. The author proposed that although SMFs promoted the reactive oxygen species (ROS) level in the first, they also accelerate antioxidative enzymes activation later. This combined actions finally caused negligible changes in hearing loss (Politański et al. 2010). The oxidative stress in rat cortex brain and hippocampus also increased under the combined effect of SMF and cadmium (Cd) (Amara et al. 2011). Moreover, although a 128 mT SMF exposure had no effect on epididymal sperm count, spermatozoa motility, or genital organ weight after 30-day exposure (Amara et al. 2006a), zebrafish exposed to 2.5, 5, 7.5 mT had increased levels of cortisol and decreased sex hormone concentrations (Sedigh et al. 2019). Therefore, as we have discussed recently, more research is needed on the effects of electromagnets on the reproductive system (Song et al. 2022). Moreover, the effects of SMFs on hematological parameters are also inconsistent. For both 128 mT SMFs, Amara et al. found that subacute exposure (1 h/day, 5 days) did not change hematological parameters but 30-day consecutive exposure significantly increased hemoglobin, red blood cells, white blood cells, and platelet number (Amara et al. 2006b). While Elferchichi et al. found that SMF 1 h/day for 15 consecutive days decreased red blood cell count, hemoglobin, and hematocrit values (Elferchichi et al. 2016).

The effects of SMFs generated by MRI were also different. Pregnant mice were exposed at the bore entrance (1.5 T and 7 T, 75 min/day, 18 days) during the entire period of pregnancy, and no effect was observed with pregnancy rate,

Table 14.3 Intermittent exposure

Subjects	Magnet	SMF flux density	Period of time	Effects	References
Sprague-Dawley rats	Electromagnet	0.004 T	2 h/day, 16 weeks	Prevent bone architectural deterioration and strength reduction in T1DM rats	Zhang et al. (2018)
C57BL/6 mice		0.005 T	8 h on the first day, then 2 h/day, 14 days	No damage to hearing loss	Politański et al. (2010)
Zebrafish		0.0025, 0.005, 0.0075 T	1 h/day, 3 weeks	Decrease the concentration of the sex hormones	Sedigh et al. (2019)
Wistar rats		0.128 T	1 h/day, 30 days	Increase hemoglobin, red blood cells, white blood cells, and platelet number	Amara et al. (2006b)
			1 h/day, 15 days	Decrease red blood cell count, hemoglobin, and hematocrit values	Elferchichi et al. (2016)
			1 h/day, 30 days	No effect on epididymal sperm count, spermatozoa motility, and genital organ weight	Amara et al. (2006a)
				Increase oxidative stress in rat cortex brain and hippocampus	Amara et al. (2011)
Balb/c mice	Permanent magnet	Max. 0.4767 T	30 min/day, 2 weeks	Inhibit the increased sensitivity in neuropathic pain	Antal and László (2009)
CD1 mice			30 min/day, 6 weeks	Reduce blood glucose level	László et al. (2010)
C57BL/6 mice			40 min/day, 17 days	Prolongs induced preterm birth (PTB)	László and Pórszász (2011)
BALB/c mice		0.4–0.5 T	6 h/day, 38 days	Inhibit GIST-T1 tumor growth	Tian et al. (2018)
Wistar albino rats	MRI-generated SMF	50 cm from the bore opening of 1.5 T MRI	12 h/day, 8 weeks	Deteriorate bone microstructure and vitamin D metabolism	Gungor et al. (2015)
C57Bl/6J mice		1.5 and 7 T	75 min/day, 18 days	No deleterious effect on offspring	Zahedi et al. (2014)
		7 T		No changes in emotional behavior, spatial or emotional learning	Hoyer et al. (2012)
C57BL/6 mice		16.4 T	3 h/day, 2 times a week, 4 weeks	Impair the vestibular system	Tkáč et al. (2021)
			3 h/day, 2 times a week, 8 weeks		

h hour, *min* minute

malformations, sex distribution, or postpartum death of offspring (Zahedi et al. 2014), neither in emotional behavior, spatial or emotional learning (Hoyer et al. 2012). However, there are also some adverse biological effects. Chronically exposed to 16.4 T SMFs (3 h/day, 2 times a week) for 4 weeks and 8 weeks both result in impairment of the vestibular system in mice (Tkáč et al. 2021). And the night period exposure (12 h/day, 8 weeks) in the position that 50 cm from the bore opening of the magnet in 1.5 T MRI devices (about 200 mT) deteriorates bone microstructure and vitamin D metabolism, for the mean cortical thickness, the mean trabecular wall thickness, number of trabeculae per 1 mm^2, and the mean vitamin D level were lower in SMF exposure group (Gungor et al. 2015).

14.3 Human Studies

Because of experimental limitation, ethical restriction and regulations, there are only a few studies available on human SMF long-term exposure (Table 14.4), including orthodontic tooth movement and pain relief, both of which showed no harmful, and even beneficial effects. For example, Bondemark et al. have studied the effects of SMF on human dental pulp and gums. First in 1995, they found that the first maxillary premolar and adjacent gingival tissue exposed to a bonded magnet with a max. magnetic flux density of 0.09 T did not cause any histologically detectable changes in human pulp or gums after 8-week exposure in seven individuals (Bondemark et al. 1995). In 1998, they bonded magnets with slightly higher intensities to the buccal surface of the upper premolars of eight subjects for 9 months and found SMFs did not influence human buccal mucosa (Bondemark et al. 1998). In 2003, Weintraub et al. randomly assigned 375 patients with II or III stage of diabetic peripheral neuropathy (DPN) into the experimental group wearing continuous magnetized insoles (45 mT) for 4 months. Their results showed that the magnetized insoles can reduce numbness, tingling, and exercise-induced foot pain (Weintraub et al. 2003). However, other researchers evaluated 11 subjects with vertebral deformity and back pain and found that repeated 30-min local exposure (10 times a week) to non-uniform SMF has no clinically significant effect on pain perception (Mészáros et al. 2013).

In fact, for the long-term exposure of SMF on human bodies, one of the best examples is magnetic sphincter augmentation device (MSAD), an implantable device that is used in treating gastroesophageal reflux disease (Fig. 14.1) (Ganz et al. 2016). It has been used world widely. Besides its clinical benefits for effectively treating GERD, there are also several studies conducted on the safety of this type of treatment. For example, a survey in 100 patients during a 6-year period showed that MSAD provides safe and long-term reduction of esophageal acid exposure and substantial symptom improvement (Bonavina et al. 2013). Another safety analysis of the first 1000 patients treated with MSAD also confirms the safety of this device and the implantation technique itself (Lipham et al. 2015). Moreover, a study in 85 subjects that have been implanted with this magnetic device reported no

Table 14.4 Laboratory studies on humans using permanent magnets

Subjects	SMF flux density	Exposure time	Effects	References
The premolar and adjacent gingival tissue in seven individuals	0.01–0.09 T	8 weeks, continuously	No histologically detectable changes in human pulp and gums	Bondemark et al. (1995)
The buccal surface of maxillary premolars in eight individuals	0.08–0.14 T	9 months, continuously	No increase in keratinization or other signs of surface abnormalities	Bondemark et al. (1998)
Feet of patients with diabetic peripheral neuropathy (DPN)	0.045 T	4 months, magnetized insoles, intermittently	Reduce numbness, tingling, and exercise-induced foot pain	Weintraub et al. (2003)
Patients with vertebral deformities and back pain	0.192 T	30 min/week, 10 weeks, intermittently	No clinical effect on pain	Mészáros et al. (2013)
100 patients with GERD	N/A	Median implant duration was 3 years (range 378 days–6 years)	Reduce distal esophageal acid exposure, improve sustained symptom and had no substantial or new safety issues	Bonavina et al. (2013)
1000 patients with GERD	N/A	Median implant duration was 274 days	No intraoperative complications, no device migrations or malfunctions	Lipham et al. (2015)
85 patients with GERD	N/A	5 years	No device erosions, migrations, or malfunctions and improve the anti-reflux barrier	Ganz et al. (2016)

new safety risks in 5 years and it works efficiently in improving the anti-reflux barrier (Ganz et al. 2016).

14.4 Epidemiological Studies

Although most animal and human studies showed no effects, or even beneficial effects of long-term SMF exposure, it is interesting and worrisome that some research in the form of questionnaires indicates some potential risks (Table 14.5). For example, a survey on the relationship between MRI-generated SMF exposure and hypertension shows that the occurrence of hypertension may be related to SMF exposure (Bongers et al. 2018). Schaap et al. also observed a positive correlation between the magnetic field strength of MRI scanner and the reported symptoms

Table 14.5 Epidemiological studies with occupational exposure to MRI

Research objects	SMF flux density	Effects	References
361 employees of 14 clinical and research MRI facilities	1.5 T, 3.0 T and 7.0 T	Observe a positive association between scanner strength and reported symptoms, such as vertigo	Schaap et al. (2014)
Male workers of an MRI-manufacturing facility	Cumulative SMF exposure ≥7.4 K tesla minutes	The occurrence of hypertension may be related to SMF exposure	Bongers et al. (2018)
120 MRI personnel	As high as 0.5 T	Had a higher proportion of symptoms such as headaches, sleep problems, palpitations, fatigue, and attention problems	Ghadimi-Moghadam et al. (2018)

(mainly vertigo) among the workers using MRI scanners of 1.5 T, 3.0 T, and 7.0 T (Schaap et al. 2014). Ghadimi et al. designed a questionnaire to collect information from 120 MRI personnel, the study showed increased frequencies of adverse effects in MRI workers, who had a higher proportion of symptoms, such as headaches, sleep problems, palpitations, fatigue, and attention problems than control group (Ghadimi-Moghadam et al. 2018). These surveys indicate that occupational exposure to SMFs might have some correlations to the appearance of health problems, and magnetic flux density seems to be a main influencing factor compared with exposure time. However, these studies did not consider other confounding variables including environmental contaminants, as well as the potential bias of the MRI workers.

14.5 Discussions

We have summarized the reported studies of long-term SMF effects by the exposure method. It is interesting that there are some differences between continuous exposure and intermittent exposure. Continuous SMFs exposure mostly showed either negligible or even beneficial effects while the results of intermittent exposure are highly variable. We think there are mainly two reasons.

Firstly, due to the limitations of experimental set up, most continuous SMF exposure experiments have used permanent magnets. However, the intermittent exposure experiments have used various magnets. It is interesting that the adverse effects are usually correlated with electromagnets, but not permanent magnets. Considering the fact that electromagnetic devices may cause additional heat, noise and weak electric field, it is difficult so far to determine whether some of the reported adverse effects were generated by these confounders. Also due to the limitations of experimental setup, most continuous SMF exposure experiments have used moderate SMF while the SMFs of intermittent exposure are highly variable. It is not surprising that higher SMF intensity could generate more effects compared to lower field.

Secondly, we hypothesize that maybe the general adaptation syndrome (GAS) is involved. It has been shown that the intensity of an organism's response to a stressful stimulus fluctuates with time, which was described as GAS. The stimulus occurs only once in continuous exposure, but in intermittent exposure the stimulations occur repeatedly, which may make the biological system very difficult to return to homeostasis. We propose this hypothesis because we found it interesting that even using the same type of magnetic field device and same magnetic field intensity, it was shown that the effects of continuous and intermittent exposure to alternating magnetic fields are also different. A study showed that the intermittent electromagnetic fields (1 min ON/OFF cycles, repeated 10 times every 2 h, 6 times/day during 48 h) in combination with NO increased cell death, but the continuous exposure (48 h) in combination with NO did not induce significant increase in cell death (Boland et al. 2002). In 1993, researchers studied the influence of 45-Hz magnetic fields on the brain functions. Ten volunteers were exposed to a continuous field and ten received an intermittent exposure (1 s ON/OFF cycles) for 1 h. Most of the changes in the measurements of electroencephalograph (EEG) were observed after intermittent exposure. Continuous exposure with the same amplitude and frequency produced no significant changes (Lyskov et al. 1993).

For human studies, it is interesting that although current experimental results showed no adverse effects, the epidemiological studies using questionnaires for MRI workers have reported the appearance of hypertension, headaches, sleep problems, and other health problems. We think there are at least four reasons. First of all, the magnetic field in MRI is higher than most experimental studies, and MRI workers standing by the machine are exposed to gradient SMFs. These both could cause more significantly effects. Secondly, most MRI workers take the survey have worked with the MRI machines for years so that the exposure time is much longer. Thirdly, since MRI workers are repeatedly and intermittently exposed to magnetic fields, the general adaptation syndrome that we mentioned above may contribute to the symptoms reported. Last but not the least, the questionnaires cannot exclude psychological factors.

However, it should be mentioned that although reported studies showed that most long-term SMF treatment did not cause serious harmful effects to animals or humans, we still need to pay extra attention and perform a lot more investigation. In fact, we recently found that even moderate SMF of some specific parameter generated by permanent magnets may also produce harmful effects at some special conditions. For example, we recently found that the health condition of mice that have consumed a large amount of alcohol (heavy drinking) was deteriorated by weeks of continuously exposure to upward SMFs of ~0.1 T with magnetic flux of ~4.5×10^{-3} Wb provided by permanent magnet plate, but not by the downward direction (Song et al. Our lab unpublished data). In contrast, when using healthy mice and the same sets of SMF devices, their health conditions are not harmed even after years of continuous exposure. In fact, their health conditions are even improved (Fan et al. Our lab unpublished data). The health conditions of mice drinking lower amount of alcohol were also improved by these SMF devices. Moreover, as mentioned before, the SMF effects on mice with different blood pressure level before exposure are totally different. Therefore, the subject's status is a very important factor that determines the SMF exposure consequences. Moreover, it was reported that 0.7 T SMF exposure for 35 days could cause sperm heads abnormality, which should also cause some attention and more investigations (Tablado et al. 1998).

14.6 Conclusion

In this chapter, we have reviewed the biological effects of animals and humans that are exposed to SMFs for over 2 weeks, either continuously or intermittently. Most studies were carried out in animals, which indicate that long-term moderate SMF exposure could positively function in pain relief, bone formation promotion, blood pressure, and blood glucose regulation. Although the reported studies for humans are not very abundant, current studies focused on moderate SMFs, which seem to have some positive effects too. However, epidemiological studies, most of which used questionnaires, indicate potential mild negative effects although the influence of psychological factors was not ruled out. More double-blinded studies are encouraged to investigate the effects of long-term exposure, which will help to promote the safe application of SMFs in health and medicine.

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