CHAPTER 2

LITERATURE REVIEW

Migraine is a group of familial disorders with a genetic component. Familial hemiplegic migraine is an autosomal dominant disorder and associated with attacks of migraine with and without aura, and hemiparesis. The gene has been mapped to chromosome 19p3 in about two-thirds of cases. The defect is caused by at least ten different missense mutations in the *CACNA1A* gene. The codes for the α1 subunit of a voltage are dependent on the P/Q calcium channel, P-type neuronal calcium channel mediate 5-HT and excitatory neurotransmitter release. Voltage – Gated P/Q-type calcium channel mediate glutamate releases were involved in cortical spreading depression and might be integral in initiating the migraine aura. A second gene was mapped to chromosome 1q21-23. The defect was a new mutation in the α2 subunit of the sodium/potassium pump [35].

2.1 Pathophysiology of migraine

Migraine is a complex disorder including neuronal and vascular disturbances. The headache starts in the central nervous system by activation of the brainstem migraine generator or cortical spreading depression (CSD). These disturbances lead to neurogenic vasodilatation within the dura mater. Vasodilatation and release of proinflammatory substances lead in turn to sensitization of peripheral and central

neurons within the trigeminal system, and dura plasma protein extravasation also plays a role in migraine pathophysiology [36].

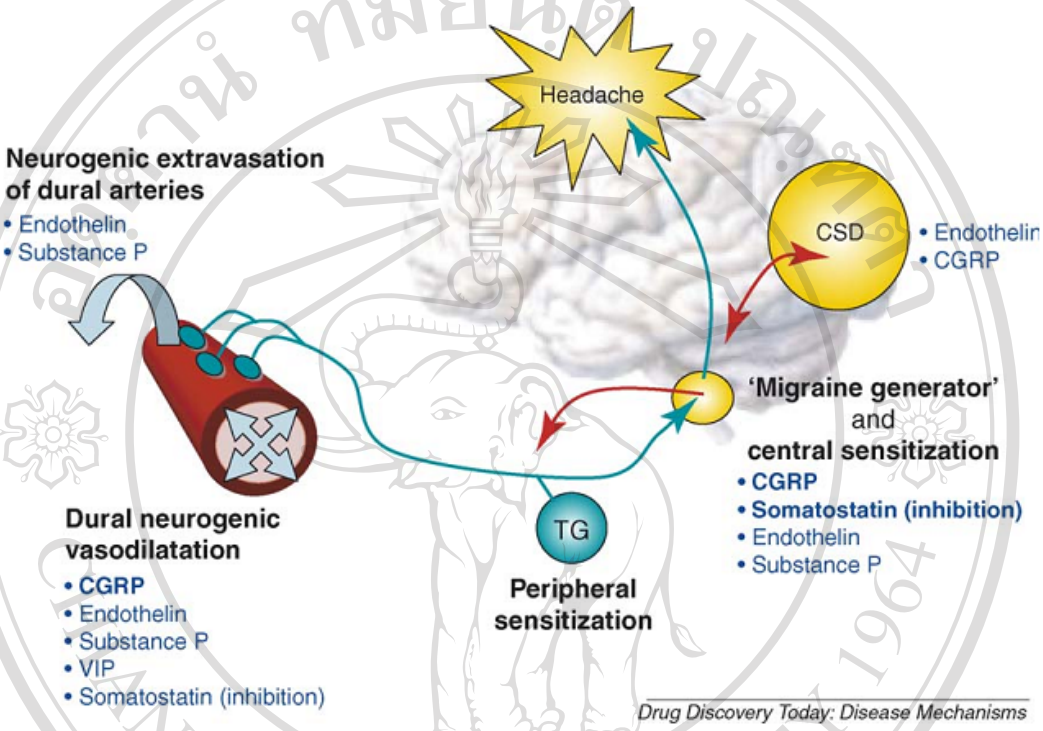

Figure 2.1 Role of neuropeptides in the pathophysiology of migraine.

(Source: Stefan Just et al. Drug Discovery Today: Disease Mechanisms 2006)

The migraine with aura may be due to neuronal hyperexcitability, and was formerly believed to be caused by cerebral vasoconstriction; and the migraine headache by reactive vasodilation. It was thought that the migraine with aura was due to neuronal dysfunction and not ischemic. The migrainous fortification spectrum corresponded to an event that moved the CSD across the cortex at 2-3 mm/min. CSD was characterized by shifts in cortical steady-state potential, transient increases in

potassium, nitric oxide (NO) and glutamate and transient increases in cerebral blood flow followed by sustained decreases. Headache probably resulted from the activation of meningeal and blood vessel nociceptors combined with change in central pain modulation. Headache and its associated neurovascular changes were subserved by the trigeminal system [1].

Trigeminal sensory neurons contained substance P, calcitonin gene-related peptide (CGRP), and neurokinin A. Stimulation resulted in release of substance P and CGRP from sensory C-fibre terminals and neurogenic inflammation. The neuropeptides interacted with the blood vessel wall and produced dilation, plasma protein extravasation, and platelet activation. The relation between CSD and headache in migraine with aura is due to CSD released hydrogen ions (H+), potassium ions (K+), and other agents including arachidonic acid (AA) and NO in the extracellular space of the neocortex. These agents diffused towards local blood vessels and depolarised perivascular trigeminal terminals, and in turn caused activation of the caudal portion of trigeminal nucleus (TGN) in the brainstem. At the same time, collateral axons of activated neurons in the trigeminal ganglion (TGG) released proinflammatory peptides in the meninges and their vessels, leading to a local inflammatory reaction. The activation of TGN was caused by CSD produced vasodilations of meningeal vessels through a pathway origin from the superior sagital sinus (SSN), reaching meningeal blood vessels via the sphenopalatine ganglion (SPG). The perception of pain was mediated by higher-order projections from the TGN [35, 37].

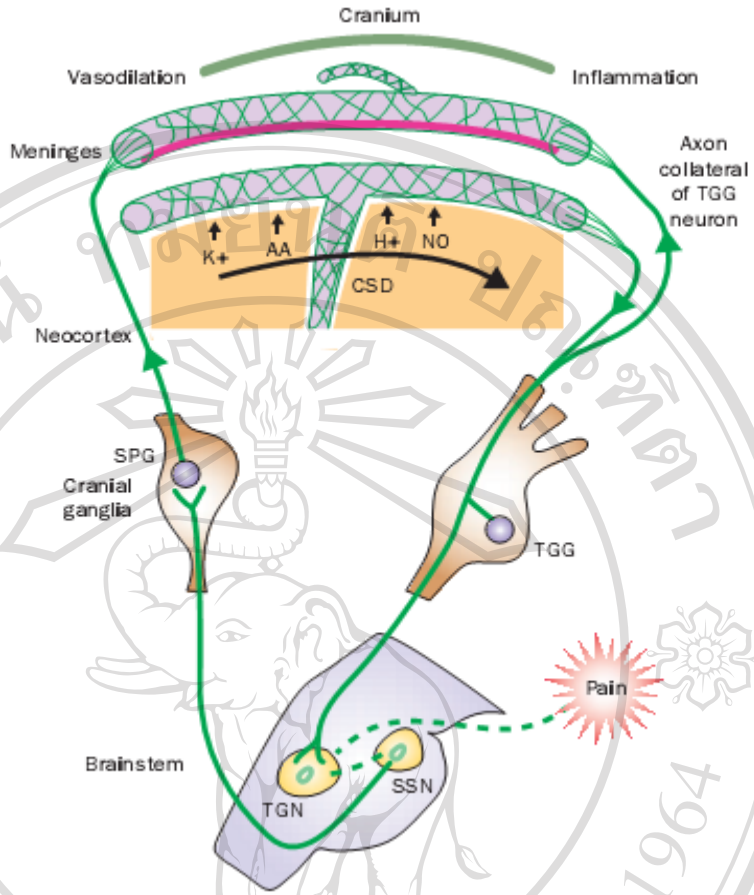

Figure 2.2 Cortical spreading depression: The relationship between cortical spreading depression (CSD) and headache in migraine with aura.

(Source: Silberstein SD. SEMINAR on Migraine. Lancet 2004; 363: 381–91.)

Substances released into the perivascular space during CSD, including K+ and glutamate, might activate first-order neuron nerve endings and cause transient hyperemia and vasodilation, especially in the cortex, pial and dural vessels. Second-order neurons relay the pain signal not only to high brain centres such as the thalamus, but also parasympathetic efferent fibres via the superior salivatory nucleus and

superior sphenopalatine ganglion (SPG). Upon stimulation, these fibres released vasoactive intestinal peptides (VIP), NO, and acetylcholine (Ache). VIP and NO were potent vasodilators responsible for the delayed vasodilation of cerebral arteries during migraine attack. In humans, SPG blocked during acute attacks partially relieved headache pain, but not cutaneous hyperalgesia and allodynia. Activation of second-order neurons was measurable in trigeminal nucleus pars caudalis (TNC) cell bodies, as enhanced electrical activity or increased expression of marker proteins for neuronal activation. If sensitized, TNC neurons also showed enhanced sensitivity to sensory fibres from the periorbital skin converging at the same neuron. This explained development of cutaneous allodynia [24]. The intracranial vessels were the only source for eliciting intracranial pain and particularly referred to pain as it occurred in primary headache. The intracranial blood vessels were supplied with nerve fibres that emanated from cell bodies in ganglion belonging to the sympathetic, parasympathetic and sensory nervous systems [38].

2.2 Diagnosis of Migraine

Diagnostic criteria for migraine were based on those of the International Headache Society (IHS). The International Headache Society classification criteria for migraine diagnosis were revised in 2004, with migraine divided into 2 major sub-types [34]:

2.2.1 Migraine without aura (common migraine)

Description:

Recurrent headache disorder manifesting in attacks lasting 4-72 hours, with typical characteristics of unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

A. At least 5 attacks fulfilling criteria B-D

B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)

C. Headache with at least two of the following characteristics:

1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation or cause by avoidance of routine physical activity (e.g. walking or climbing stairs)

D. Headache with at least one of the following symptoms:

1. nausea and/ or vomiting
2. photophobia and phonophobia

E. No attribution to another disorder.

2.2.2 Migraine with aura (classical migraine)

Description:

Recurrent headache disorder manifesting in attacks of reversible focal neurological symptoms, which usually develop gradually over 5-20 minutes

and last for less than 60 minutes. Headache with the features of migraine without aura usually follow aura symptoms. A lack of migrainous features or their complete absence is rarely common in this headache.

Diagnostic criteria:

A. At least 2 attacks fulfilling criterion B

B. Migraine aura fulfilling criteria B and C for one of the sub-forms 1.2.1-1.2.6

C. No attribution to another disorder.

2.2.3 Typical aura with migraine headache

Description:

Typical aura consisting of visual and/or sensory and/or speech symptoms that gradually develop in no longer than one hour, with a mix of positive and negative features and complete reversibility, which characterize the aura associated with the headache fulfilling criteria for 1.1 *Migraine without aura*.

Diagnostic criteria:

A. At least 2 attacks fulfilling criteria B-D

B. Aura consisting of at least one of the following, but no motor weakness:

1. fully reversible visual symptoms including positive features (e.g. flickering light, spots or lines) and/or negative features (i.e. loss of vision)
2. fully reversible sensory symptoms including positive features (i.e. pins and needles) and/or negative features (i.e. numbness)

3. fully reversible dysphasic speech disturbance

C. At least two of the following:

1. homonymous visual symptoms and/or unilateral sensory symptoms
2. at least one aura symptom developing gradually over ≥5 minutes and/or different aura symptoms occurring in succession over ≥5 minutes
3. each symptom lasting ≥5 and ≤ 60 minutes

D. Headache fulfilling criteria B-D for 1.1 *Migraine without aura* and beginning during or following the onset of aura within 60 minutes

E. No attribution to another disorder.

2.2.4 Typical aura with non-migraine headache

Description:

Typical aura consisting of visual and/or sensory and/or speech symptoms that gradually develop in no longer than one hour, with a mix of positive and negative features and complete reversibility, which characterize the aura associated with the headache fulfilling criteria for 1.1 *Migraine without aura*.

Diagnostic criteria:

A. At least 2 attacks fulfilling criteria B-D

B. Aura consisting of at least one of the following, but no motor weakness:

1. fully reversible visual symptoms including positive features (e.g. flickering light, spots or lines) and/or negative features (i.e. loss of vision)

2. fully reversible sensory symptoms including positive features (i.e. pins and needles) and/or negative features (i.e. numbness)
3. fully reversible dysphasic speech disturbance

C. At least two of the following:

1. homonymous visual symptoms and/or unilateral sensory symptoms
2. at least one aura symptom developing gradually over ≥5 minutes and/or different aura symptoms occurring in succession over ≥5 minutes
3. each symptom lasting ≥5 and ≤ 60 minutes

D. Headache that did not fulfill criteria B-D for 1.1 *Migraine without aura* beginning during or following the onset of aura within 60 minutes

E. No attribution to another disorder.

2.2.5 Typical aura without headache

Description:

Typical aura consisting of visual and/or sensory symptoms with or without speech symptoms, gradually developing over no longer than one hour, with a mix of positive and negative features and complete reversibility, which characterize the aura not associated with headache.

Diagnostic criteria:

A. At least 2 attacks fulfilling criteria B-D

B. Aura consisting of at least one of the following, with or without speech disturbance, but no motor weakness:

1. fully reversible visual symptoms including positive features (e.g. flickering light, spots or lines) and/or negative features (i.e. loss of vision)
2. fully reversible sensory symptoms including positive features (i.e. pins and needles) and/or negative features (i.e. numbness)

C. At least two of the following:

1. homonymous visual symptoms and/or unilateral sensory symptoms
2. at least one aura symptom developing gradually over ≥5 minutes and/or different aura symptoms occurring in succession over ≥5 minutes
3. each symptom lasting ≥5 and ≤ 60 minutes

D. Headache not occurring during or following the onset of aura within 60 minutes

E. No attribution to another disorder.

2.2.6 Familial hemiplegic migraine (FHM)

Description:

Migraine patient with aura including motor weakness, and one first- or second-degree relative, who has the same signs and symptoms.

Diagnostic criteria:

A. At least 2 attacks fulfilling criteria B and C

B. Aura consisting of fully reversible motor weakness and at least one of the following:

1. fully reversible visual symptoms including positive features (e.g. flickering light, spots or lines) and/or negative features (i.e. loss of vision)
2. fully reversible sensory symptoms including positive features (i.e. pins and needles) and/or negative features (i.e. numbness)
3. fully reversible dysphasic speech disturbance

C. At least two of the following:

1. at least one aura symptom developing gradually over ≥5 minutes and/or different aura symptoms occurring in succession over ≥5 minutes
2. each aura symptom lasting ≥5 and ≤ 24hours
3. headache fulfilling criteria B-D for 1.1 *Migraine without aura* beginning during or following the onset of aura within 60 minutes

D. At least one first- or second-degree patient relative, who had had attacks fulfilling criteria A-E

E. No attribution to another disorder.

2.2.7 Sporadic hemiplegic migraine

Description:

Migraine patient with aura including motor weakness, but no first- or second-degree relative having the same signs or symptoms.

Diagnostic criteria:

A. At least 2 attacks fulfilling criteria B and C

B. Aura consisting of fully reversible motor weakness and at least one of the following:

1. fully reversible visual symptoms including positive features (e.g. flickering light, spots or lines) and/or negative features (i.e. loss of vision)
2. fully reversible sensory symptoms including positive features (i.e. pins and needles) and/or negative features (i.e. numbness)
3. fully reversible dysphasic speech disturbance

C. At least two of the following:

1. at least one aura symptom developing gradually over ≥5 minutes and/or different aura symptoms occurring in succession over ≥5 minutes
2. each aura symptom lasting ≥5 and ≤ 24hours
3. headache fulfilling criteria B-D for 1.1 *Migraine without aura* beginning during or following the onset of aura within 60 minutes

D. No first- or second-degree patient relative with attacks fulfilling criteria A-E

E. No attribution to another disorder.

2.2.8 Basilar-type migraine

Description:

Migraine with aura symptoms clearly originating from the brain stem and/or both hemispheres simultaneously, but no motor weakness.

Diagnostic criteria:

A. At least 2 attacks fulfilling criteria B-D

B. Aura consisting of at least two of the following fully reversible symptoms, but no motor weakness:

1. dysarthria
2. vertigo
3. tinnitus
4. hypacusia
5. diplopia
6. simultaneous visual symptoms in both temporal and nasal fields of both eyes
7. ataxia
8. decreased level of consciousness
9. simultaneous bilateral paraesthesias

C. At least one of the following:

1. at least one aura symptom developing gradually over ≥5 minutes and/or different aura symptoms occurring in succession over ≥5 minutes
2. each aura symptom lasting ≥5 and ≤ 60 minutes

D. Headache fulfilling criteria B-D for 1.1 *Migraine without aura* beginning during or following the onset of aura within 60 minutes

F. No attribution to another disorder.

Other migraine sub-types consisted of 1.3-1.6, which were coded according to the International Headache Society classification criteria:

1.3 Periodic childhood syndromes that were common precursors of migraine

1.3.1 Cyclical vomiting

1.3.2 Abdominal migraine

1.3.3 Benign paroxysmal vertigo in children

1.4 Retinal migraine

1.5 Complication of migraine

1.5.1 Chronic migraine

1.5.2 Status migraine

1.5.3 Persistent aura without infarction

1.5.4 Migrainous infarction

1.5.5 Migraine-triggered seizure

1.6 Probable migraine

1.6.1 Probable migraine without aura

1.6.2 Probable migraine with aura

1.6.3 Probable chronic migraine

2.3 Treatment for migraine

Migraine treatment can be divided into non pharmacologic and pharmacologic therapies. Non pharmacologic therapies include educating the patient about the disorder, its mechanisms, approaches to treatment, and changes in lifestyle in order to avoid the triggers of migraine. In patients with migraine, the brain does not seem to

tolerate the peaks and troughs of life well. Thus, regular sleep and meals, exercise, avoiding stressful peaks and troughs while relaxing, and avoiding dietary triggers could be helpful [39, 40].

Pharmacotherapy could be acute or preventive and some patients might need both approaches [40]:

2.3.1 Treatment of acute migraine headaches

Acute treatment in an attempt to reverse or stop a headache progression once it has started is appropriate for most attacks, but it should be restricted to 2-3 days a week. Acute treatment can be specific (ergots and triptans), or non-specific (analgesics and opioids) (Table 1). Non-specific drugs control the pain of migraine, whereas specific drugs are effective in migraine headache attacks, but not useful for non-headache pain disorders.

2.3.2 Preventive treatment for migraine

Prophylactic treatment was designed to reduce attack frequency, duration and severity. Preventive drug groups include β-adrenergic blockers, antidepressants, calcium-channel antagonists, serotonin antagonists, anticonvulsants, and non-steroidal anti-inflammatory drugs. Choice is based on effectiveness, adverse events, and coexistent and co-morbid conditions (Table 1). Every drug should be started at a low dose and increased slowly until therapeutic effects develop or the maximum dose is reached. A full therapeutic trial could take 2-6 months. Acute headache drugs should

not be overused. If headaches are well controlled, treatment can be tapered and discontinued.

However, behavioral and psychological interventions are used for prevention including relaxation training, thermal biofeedback combined with relaxation training, electromyography biofeedback, and cognitive-behavioral treatment. This would be helpful in conditional co-therapy with prophylactic treatment for migraine.

In recent years, botulinum toxin has been discussed for the treatment of pain, including headache, especially chronic daily headache disorders such as transformed (or chronic) migraine, chronic tension-type headache, new daily persistent headache, and hemicrania continua. Some studies suggested that botulinum toxin type A (BT-A) might be an effective and safe prophylactic treatment for a variety of moderate to severe chronic headache types, whereas others showed results that found the efficacy of BT-A in preventing migraine headache attacks controversial. Today, studies are ongoing both with botulinum toxin A and botulinum toxin B for headache treatment (41, 42, 43, 44, 45).

Table 2.1 Drugs for acute migraine and prevention: efficacy, adverse effects, relative contraindications, and indications [35]

	Contraindications	Indication
Acute migraine		
Acetaminophen (paracetamol)	Liver disease	Pregnancy
Aspirin	Kidney disease, ulcer disease, peptic ulcer disease, gastritis (age <15 years)	Coronary artery disease, transient ischaemic attack
Non-steroidal anti-inflammatory drugs	Kidney disease, peptic ulcer disease, gastritis	Arthritis
Butalbital, caffeine, and analgesics	Use of other sedative, history of medication overuse	
Caffeine adjuvant	Sensitivity to caffeine	
Isometheptene	Uncontrolled hypertension, coronary artery disease, peripheral vascular disease	
Opioids	Drug or substance misuse	Pregnancy, rescue medication
Neuroleptics	Parkinson's disease, prolonged QTc	Nausea, vomiting, pregnancy, rescue
Dihydroergotamine		
Injections	Coronary artery disease, peripheral vascular disease, uncontrolled hypertension	Prominent nausea or vomiting
Intranasal	Coronary artery disease, peripheral vascular disease, uncontrolled hypertension	Prominent nausea or vomiting
Ergotamine		
Tablets	Prominent nausea or vomiting	
Suppositories	Coronary artery disease, peripheral vascular disease, uncontrolled hypertension	
Triptans*	Coronary artery disease, peripheral vascular disease, uncontrolled hypertension	
Preventive drugs		
β blockers	Asthma, depression, congestive heart failure, Raynaud's disease, diabetes	Hypertension, angina
Antiserotonin		
Pizotifen	Obesity	
Methysergide	Angina, peripheral vascular disease	Orthostatic hypotension
Calcium-channel blockers		
Verapamil	Constipation, hypotension	Migraine with aura, hypertension, angina, asthma
Flunarizine	Parkinson's disease	Hypertension, FHM
Antidepressants		
Tricyclic antidepressants	Mania, urinary retention, heart block	Other pain disorders, depression, anxiety disorders, insomnia
Serotonin specific reuptake inhibitor	Mania	Depression, obsessive-compulsive disorder
Monoamine oxidase inhibitors	Unreliable patient	Refractory depression
Anticonvulsants		
Divalproex/valproate	Liver disease, bleeding disorders	Mania, epilepsy, anxiety disorders
Gabapentin	Liver disease, bleeding disorders	Mania, epilepsy, anxiety disorders
Topiramate	Kidney stones	Mania, epilepsy, anxiety disorders
Non-steroidal anti-inflammatory drugs (Naproxen)	Ulcer disease, gastritis	Arthritis, other pain disorders

*Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, zolmitriptan (tablets or intranasal), sumatriptan (subcutaneous injection, intranasal, or tablets).

2.4 Health risks from the use of mobile phones

Wireless communication links have been used worldwide for many years as solutions for connectivity in point-to-point and point-to-multipoint applications. The most common wireless solutions included AM and FM radio, television broadcast stations, mobile and cellular phones, radar and microwave systems. The potential health hazards could be linked to excessive exposure to high-power densities of non-ionizing radiation. These health hazards included cancer, tumors, headache, fatigue, Alzheimer's disease, and Parkinson's disease. The frequency bands and average radiated power for cellular, personal communication systems (PCS), hand-held radios and cordless telephones are shown in Table 2.2 [46].

Table 2.2 Typical portable/mobile radio equipment [46]

Type of mobile radio	Frequency (MHz)	Average radiated power
Cellular/PCS*	824-849 MHz/1850-1990 MHz	A few hundred milliwatts
Two-way, hand-held (walkie-talkie)	30, 50, 150, 450 and 800 MHz bands	Between 2 and 5 watts
Cordless telephone	49, 915, 2450 MHz	Tens of milliwatts

* PCS: Personal Communication Systems

Around the world, a variety of other frequencies are used for both analog and digital hand-held transceivers and mobile radios, and other names were given to the systems. The most common frequencies were 800-900 MHz (analog and digital) and 1,800-2,200 MHz (digital). However, existing hand-held transceivers use frequencies from as low as 45 MHz to as high as 2,500 MHz. Power output from hand-held units seldom exceed 2 W, but power output from vehicle-mounted units such as those used by law enforcement personnel could be as high as 100 W [47].

There are many technical differences between different types of "mobile" phones. However, for evaluation of possible health hazards, the only distinction that matters is the slightly different frequencies they are operated at. The radiofrequency (RF) energy from some base stations (e.g. those for the older 800 MHz mobile phones used in the U.S.) may be absorbed somewhat more by humans than that from other types of base stations (e.g. those for the 1,800-2,000 MHz "PCS" phones used in the U.S.). However, once the energy is absorbed the effects are the same [48, 49].

At lower frequencies, such as those used by mobile phones and their base stations, the energy of the particles is much too low to break chemical bonds. Thus, RF energy is "non-ionizing". Because non-ionizing radiation cannot break chemical bonds, there is no similarity between the biological effects of ionizing radiation (x-rays) and RF energy [49, 50].

2.4.1 What is radiofrequency (RF) energy [51]?

Radiofrequency (RF) energy is another name for radio waves. It is one form of electromagnetic energy that makes up the electromagnetic spectrum. Some other

forms of energy in the electromagnetic spectrum are gamma rays, x-rays and light. Electromagnetic energy (or electromagnetic radiation) comprises waves of electric and magnetic energy moving together (radiating) through space. The area where these waves are found is called an electromagnetic field (EMF).

All electromagnetic waves travel at the speed of light. The wavelength is the distance covered by one cycle of a wave. The frequency is the number of waves passing a given point in one second. For any electromagnetic wave, the wavelength multiplied by the frequency equals the speed of light. The frequency of an RF signal is usually expressed in units called hertz (Hz). One Hz equals one wave per second. One kilohertz (kHz) equals one thousand waves per second, one megahertz (MHz) equals one million waves per second, and one gigahertz (GHz) equals one billion waves per second.

RF energy includes waves with frequencies ranging from about 3,000 waves per second (3 kHz) to 300 billion waves per second (300 GHz). Microwaves are a subset of radio waves that have frequencies ranging from around 300 million waves per second (300 MHz) to three billion waves per second (3 GHz).

2.4.2 How is radiofrequency energy used [51]?

Probably, the most important use of RF energy is for telecommunications. Radio and TV broadcasting, wireless phones, pagers, cordless phones, police and fire department radios, point-to-point links and satellite communications all rely on RF energy.

Other uses of RF energy include microwave ovens, radar, industrial heaters and sealers, and medical treatments. RF energy, especially at microwave frequencies, can heat water. Since most food has high water content, microwaves can cook food quickly. Radar relies on RF energy to track cars and airplanes as well as for military applications. Industrial heaters and sealers use RF energy to mold plastic materials, glue wood products, seal leather items such as shoes and pocketbooks, and process food. Medical uses of RF energy include pacemaker monitoring and programming.

2.4.3 How is radiofrequency radiation measured [51]?

RF waves and fields have both electrical and magnetic components. It is often convenient to express the strength of the RF field in terms of each component. For example, the unit "volts per meter" (V/m) is used to measure the electric field strength, and the unit "amperes per meter" (A/m) is used to express the magnetic field strength. Another common way to characterize an RF field is by means of the power density. Power density is defined as power per unit area. For example, power density can be expressed in terms of milliwatts (one thousandth of a watt) per square centimeter [(mW/cm2 or microwatts (one millionth of a watt) per square centimeter ($\mu W/cm^2$)].

The quantity used to measure how much RF energy is actually absorbed by the body is called the Specific Absorption Rate (SAR). The SAR is measured at the rate of RF energy absorption. It is usually expressed in units of watts per kilogram (W/kg) or milliwatts per gram (mW/g).

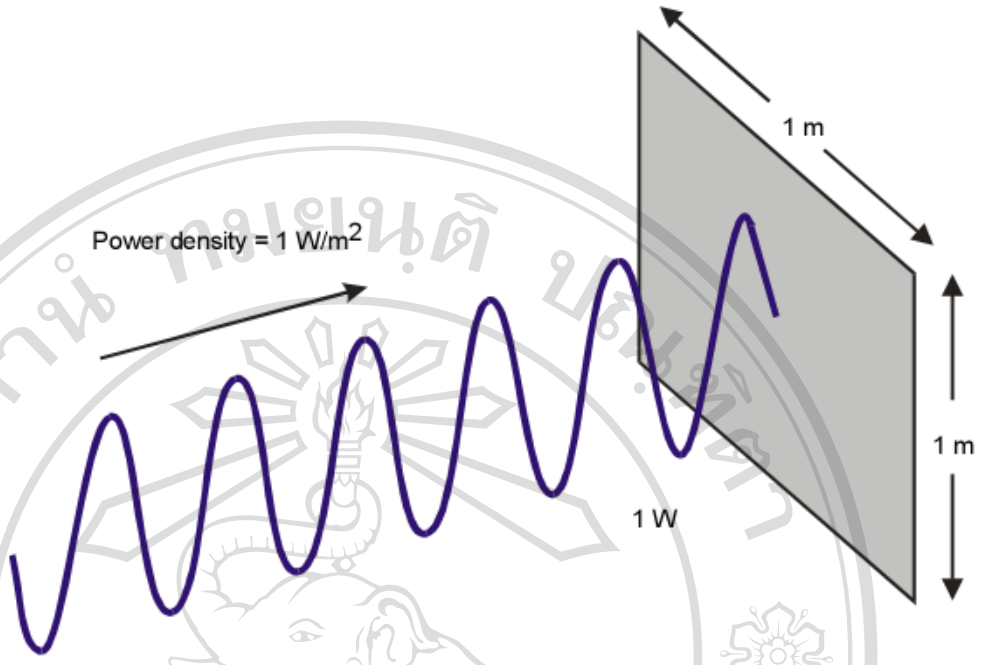

Figure 2.3 Electromagnetic wave passing through 1 m^2. If the power passing through the area is 1 W, the wave has an intensity or power density of 1 W/m^2.

(Source: Independent Expert Group on Mobile Phones. Mobile phones and health. Chilton, 2000)

2.4.4 What biological effects can be caused by RF energy [51]?

The biological effects of radiofrequency energy should not be confused with the effects from other types of electromagnetic energy.

Very high levels of electromagnetic energy, such as those found in X-rays and gamma rays can ionize biological tissues. Ionization is a process where electrons are

stripped away from their normal locations in atoms and molecules. It can permanently damage biological tissues including DNA, the genetic material. Ionization only occurs with very high levels of electromagnetic energy such as X-rays and gamma rays. Often, the term radiation is used when discussing ionizing radiation (such as that associated with nuclear power plants).

The energy levels associated with radiofrequency energy, including both radio waves and microwaves, are not great enough to cause the ionization of atoms and molecules. Therefore, RF energy is a type of non-ionizing radiation. Other types of non-ionizing radiation include visible light, infrared radiation (heat) and other forms of electromagnetic radiation with relatively low frequencies.

Large amounts of RF energy can heat tissue. This can damage tissues and increase body temperatures. Two areas of the body, the eyes and the testes, are particularly vulnerable to RF heating because they possess relatively little blood flow to carry away excess heat.

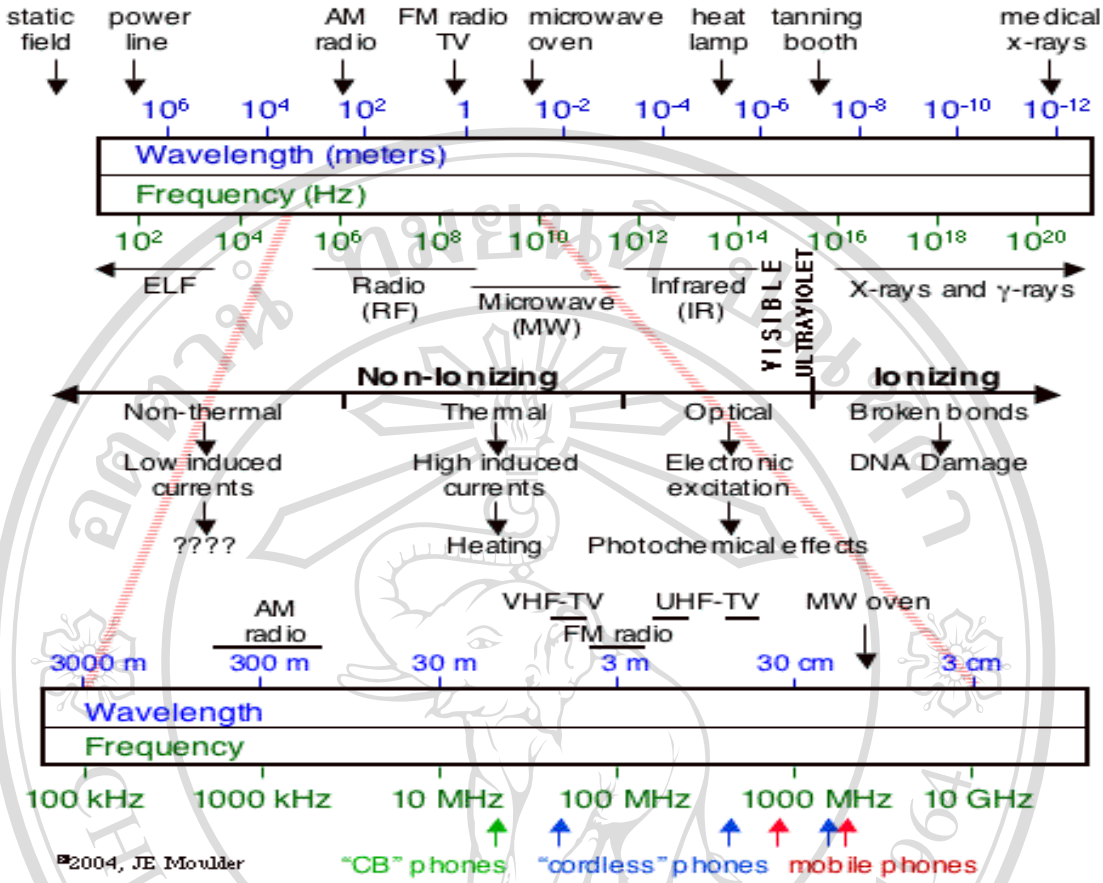

Figure 2.4 The Electromagnetic Spectrum.

(Source: Moulder JE. Mobile Phone (Cell Phone) Base Stations and Human Health. Electromagnetic Fields and Human Health 2006 at http://www.mcw.edu)

The biological effects of RF energy depend on the rate at which power is absorbed. SARs were difficult to measure on a routine basis, so the plane wave power density was usually measured. Average whole body SARs could then be calculated from the power density exposure. In this document, power density was given in mW/cm-sq (milliwatts per square centimeter). The power density guidelines were stricter for some frequencies than others because humans absorbed RF energy more at

860 MHz than at 1,800 MHz, and it was the amount of power absorbed that really mattered. Specifically, the International Commission for Non-Ionizing Radiation Protection (ICNIRP) standard was 0.40mW/cm-sq at 800 MHz and 0.90mW/cm-sq at 2,000 MHz, while the National Council on Radiation Protection and Measurements (NCRP) guidelines were 0.57mW/cm-sq and 1.00 mW/cm-sq for these frequencies. In summary, the minimum SAR for the genotoxic effects appeared to be in the 0.2-1.3 W/kg range, but there were no clear exposure-response relationships at higher SARs [49, 50].

The amount of RF radiation routinely encountered by the general public is too low to produce significant heating or increased body temperature. Still, some people have questions about the possible health effects of low level RF energy. It is generally agreed that further research is needed to determine what effects actually occur and whether they are dangerous to people. In the meantime, standards-setting organizations and government agencies are continuing to monitor the latest scientific findings to determine whether changes in safety limits are needed to protect human health [52].

2.4.5 Mechanisms of biological effects from exposure to RF [52]

The electric and magnetic fields produced in the body by a nearby electromagnetic source may cause both thermal and non-thermal biological effects. The effects of magnetic fields vary with frequency, and are probably greatest in biological tissue containing small amounts of magnetite. Magnetite (Fe_3O_4) is a naturally occurring oxide of iron. It is a ferrimagnet, but behaves similarly in

magnetic fields to a ferromagnet such as iron. Magnetite is found in certain bacteria and the cells of many animals, including human beings.

2.4.5.1 Thermal effects

Thermal effects are those caused by the rise in temperature produced by the energy absorbed from oscillating electric fields. The force produced by an electric field on charged objects, such as the mobile ions present in the body, causes them to move, resulting in electric currents, and the electrical resistance of the material in which the currents are flowing results in heating. This heat input causes the temperature to rise and it continues to do so until the heat input is balanced by the rate at which it is removed, mostly by blood flowing to and from other parts of the body. It is estimated that it takes several minutes from the moment RF exposure occurs for the irradiated parts of the body to reach their final equilibrium temperatures.

2.4.5.2 Non-thermal effects

Radiofrequency radiation could, however, produce other effects. In general, detectable changes can arise only if the effect of the electric field within the biological system exposed to RF fields is not masked by thermal noise. Thermal noise or random motion, also known as Brownian motion, is due to the thermal energy that all objects possess at temperatures above absolute zero. In solids, the atoms vibrate and in gases and liquids they move erratically to and fro following very frequent collisions with other atoms. So, all components of biological tissue – ions, molecules and cells are in constant motion. If the resonance is very sharp, it would be very much smaller than

the total thermal noise, so that quite small electric fields might produce detectable effects in resonant systems of this type, should they exist in biological tissue.

2.5 Previous relevant studies

2.5.1 Biological effects from exposure to RF radiation

Unlike the conditions in most previous researches on the biological effects of RFR, in which whole body exposure was studied, the effects of cellular telephone-related exposure involved repeated exposure with variable durations of a relatively constant amount of body tissue (i.e. part of the head). In considering the biological effects of RFR, the intensity and frequency of the radiation and exposure duration are important determinants of the responses. For repeated exposure, as in the case of cellular telephone use, homeostatic compensatory response can occur. On the other hand, since a relatively constant amount of body tissue is exposed, cumulative effect could occur and lead to an eventual breakdown of homeostasis and present adverse health consequences. Current findings in this study demonstrated a significant correlation of the amount of mobile phone use, duration of calls, and frequency of calls with the number of migraine attacks per month. Data from some of the experiments described below do suggest that RFR could have biological effects on human cells [53].

Merritt J.H. et al. [54] (1978) studied blood-brain-barrier permeability after microwave-radiation. The results showed that increased fluorescein uptake was seen only when rats were made hyperthermic in a warm-air environment. Similarly, brain

uptake of C-mannitol was not increased when using the Oldendorf dual isotope technique. It was seen as a result of exposure to pulsed 1.3-GHz radiation at peak power densities of up to 20 mW/cm^2, or in the continuous wave mode from 0.1–50 mW/cm^2. An attempt to alter the permeability of the blood-brain-barrier for serotonin with microwave radiation was unsuccessful. From these studies, it would appear that the brain must be made hyperthermic for changes to occur in permeability of the barrier induced by microwave radiation.

Later, Lin J.C. et al. [55] (1980) carried out a study on microwave and blood-brain-barrier interaction in order to investigate correlating changes of blood-brain-barrier permeability by the quantity and distribution of absorbed microwave energy inside the brain of adult Wistar rats that were anesthetized by sodium pentobarbital. Exposure to pulsed radiation of 2,450-MHz for 20 min at average power densities of 0.5, 1, 5, 20, 145 or 1,000 mW/cm^2, resulted in average specific absorption rates (SARs) in the brain of 0.04, 0.08, 0.4, 1.6, 11.5 or 80.0 mW/g, respectively. These findings did not produce staining, except in the pineal body, pituitary gland and choroid plexus regions that normally showed high permeability. Apart from these exceptional regions, staining was also absent in the brain of sham-exposed animals. The rectal temperature, as monitored by a copper-constantan thermocouple, showed a maximum increase of less than 0.75°C from a mean pre-exposure temperature of 36.6°C. The highest brain temperature recorded in a similar group of animals using a thickfilm carbon thermistor was less than 41.0°C.

In 1982, Lin J.C. et al. [56] repeated the study using the same method and conditions as mentioned above, but with differences in power density of 0.5 to 2,600 mW/cm^2 and SARs of 0.04 to 200 mW/g. The findings revealed that when the

incident power density was increased to 3,000 mW/cm^2 (SAR of 240 mW/g), extravasation of Evans blue could be seen in the cortex, hippocampus, and midbrain. The rectal temperature, as monitored by a copper-constantan thermocouple, showed a maximum increase of less than 1.0°C. The brain temperature recorded in a similar group of animals, using a non-field-perturbing thermistor, exceeded 43°C. At the higher power density, the extravasation depended on the irradiation and euthanization times. In one series of experiments, rats were irradiated at 3,000 mW/cm^2 for 5, 10, 15, and 20 min. Immediately after irradiation, all except the 5-min animals exhibited increased permeability in some regions of the brain. The brains of rats euthanized 30 min after irradiation were free of Evans blue, while those euthanized at 10 and 20 min postirradiation showed significant dye staining, but with less intensity than those euthanized immediately after irradiation.

Goldman H. et al. [57] (1984) studied cerebrovascular permeability to ^{86}Rb in rats after exposure to pulsed microwaves. Microwaves (pulsed, 2,450 MHz) were applied directly to the head at an average power density of 3 W/cm^2 for 5, 10, or 20 min, producing a peak specific absorption rate of 240 W/kg in the brain, which, after 10-min exposure, resulted in brain temperatures in excess of 43°C. When compared with unexposed controls, the uptake of ^{86}Rb increased mostly in those regions directly in the path of the irradiation, namely, the occipital and parietal cortex, as well as the dorsal hippocampus, midbrain, and basal ganglia. In a separate group of animals, regional brain-vascular spaces were found to increase with brain temperature. These results supported previous observations that indicated reliably demonstrable increases in blood-brain-barrier permeability, which were associated with intense, microwave-

induced hyperthermia, and the observed changes were not due to field-specific interaction.

Lai H. et al. [58] (1989) reported low-level microwave irradiation and central cholinergic systems. The results demonstrated that increases in choline uptake activity in the frontal cortex, hippocampus, and hypothalamus were observed after 20 min of acute microwave exposure. Tolerance to the effect of microwaves developed in the hypothalamus, but not in the frontal cortex and hippocampus of rats subjected to ten daily 20-min exposure sessions. Furthermore, the effects of acute microwave irradiation on central choline uptake could be blocked by pretreating the animals before exposure with the narcotic antagonist, naltrexone. In another series of experiments, rats were exposed to microwaves in ten daily sessions of either 20 or 45 min, and muscarinic cholinergic receptors in different regions of the brain were studied by 3H-QNB binding assay. Decreases in concentration of receptors occurred in the frontal cortex and hippocampus of rats subjected to ten 20-min microwave exposure sessions, whereas an increase in receptor concentration occurred in the hippocampus of animals exposed to ten 45-min sessions.

Lai H. et al. [59] (1995) displayed that an acute low-intensity of 2,450 MHz microwave exposure increased DNA single-strand breaks in rat brain cells by using an alkaline microgel electrophoresis method. Immediately after 2 h of exposure to pulsed (2 μs width, 500 pulses/s) microwaves, no significant effect was observed, whereas a dose rate-dependent [0.6 and 1.2 W/kg whole body specific absorption rate (SAR)] increase in DNA single-strand breaks was found in brain cells of rats at 4 h post exposure. Furthermore, increases in brain cell DNA single-strand breaks were observed immediately in rats exposed to a continuous-wave of 2,450 MHz

microwaves (SAR 1.2 W/kg) for 2 h, as well as at 4 h post exposure. Later, Lai H. et al. (1996) investigated the effects of acute (2-h) exposure on a pulsed modulated and continuous wave at 2,450-MHz radiofrequency electromagnetic radiation on DNA strand breaks in the brain cells of rats. The average spatial power density of the radiation was 2 mW/cm^2, which produced a whole-body average-specific absorption rate of 1.2 W/kg. Single- and double-strand DNA breaks in individual brain cells were measured at 4 h post-exposure using a microgel electrophoresis assay. An increase in both types of DNA strand breaks was observed after exposure to either the pulsed or continuous-wave radiation. However, no significant difference was observed between the effects of the two forms of radiation.

Persson B.R.R. et al. [60] (1997) manifested the blood-brain-barrier permeability in rats exposed to electromagnetic fields used in wireless communication. The frequency of pathological rats was significantly increased ($p <$ 0.0001) from 62/372 (ratio: 0.17 ± 0.02) for control rats to 244/630 (ratio: 0.39 ± 0.03) in all exposed rats. Grouping the exposed animals according to the level of specific absorbed energy (J/kg) gave a significant difference at all levels above 1.5 J/kg. The exposure was 915 MHz microwaves, which were pulse modulated (PW) at 217 Hz with 0.57 ms pulse width, 50 Hz with 6.6 ms pulse width or continuous wave (CW). The frequency of pathological rats (0.17) among controls in the various groups was not significantly different. The frequency of pathological rats was 170/481 (0.35 ± 0.03) among rats exposed to pulse modulation (PW) and 74/149 (0.50 ±0.07) among those exposed to continuous wave exposure (CW). These results showed a highly significant difference to the corresponding controls ($p <$0.0001), and the frequency of

pathological rats after exposure to pulsed radiation (PW) was significantly less ($p < 0.002$) than after exposure to continuous radiation (CW).

Freude G. et al. [61] (2000) studied how microwaves emitted by cellular telephones affected human slow brain potentials (SP) in two experiments, which were about 6 months apart. In the first experiment, a significant decrease of SP was found during exposure to EMF in a complex visual monitoring task (VMT). This effect was replicated in a second experiment. In addition to the VMT, EMF effects on SP were analysed in two further, less demanding tasks: in a simple finger movement task to elicit a Bereitschaftspotential (BP), and in a two-stimulus task to elicit a contingent negative variation (CNV). In comparison to the VMT, no significant main EMF effects were found in BP and CNV tasks. The results accounted for a selective EMF effect on particular aspects of human information processing, but did not indicate any influence on human performance, well-being and health.

Finnie J.W. et al. [62] (2002) reported the effect of long-term mobile communication microwave exposure on vascular permeability in mouse brain using a purpose-designed exposure system at 900 MHz. Mice were given a 60-minute far-field, whole body exposure on each of 5 days per week for 104 weeks at specific absorption rates (SAR) of 0.25, 1.0, 2.0 and 4.0 W/kg. Albumin immunohistochemistry was used to detect increased vascular permeability, and the efficacy of the vascular tracer was confirmed with a positive control group exposed to a clostridial toxin known to increase vascular permeability in the brain. The findings showed that in all exposed and control groups, albumin extravasation was minimal, often leptomeningeal, and was deemed insignificant, as a maximum of three

capillaries or venules in a given brain showed leakage from the very many blood vessels present in the three coronal brain sections.

Salford G.L. et al. [63] (2005) investigated male and female Fischer 344 rats exposed in a transverse electromagnetic transmission line chamber to microwaves of 915 MHz as a continuous wave (CW), and pulse-modulated with SAR that varied between 0.016 and 5 W/kg. The results showed albumin leakage in 5 from 62 of the controls and 56 from 184 of the animals exposed to 915 MHz microwaves. The continuous wave resulted in 14 positive findings in 35 animals, which differed significantly from the controls (P = 0.002). With pulsed 915 MHz microwaves at repetition rates of 200, 50, 16, and 8 s^{-1}; 42 of 149 animals were positive, which was highly significant at the P = 0.001 level. This revealed that both CW and pulsed 915 MHz microwaves had the potential to open up the blood-brain-barrier (BBB) for albumin passage. However, there was no significant difference between continuous and pulsed 915 MHz microwaves in this respect.

Garcia-Sagredo et al. [64] reported the effect of low-level pulsed electromagnetic fields on the human chromosome. The results showed that an increase of chromosome aberrations (CAs) in cultures under the effect of EMF at 20 and 40 G (5.17 and 6.53) was observed, when compared with the control cultures (4.59). Even so, there was a significant difference for only 40 G of EMF exposure by comparison. Moreover, data manifested a significant linear dose-response effect. In another study by Salford et al. of the GSM effect on the blood-brain-barrier in rats, high significance was evident in neuronal damage in the cortex, hippocampus, and basal ganglia in the brains of exposed rats. The effect of EMF exposure had a positive relationship of dose-response [65]. The intermittent changes of cell growth kinetics

were obtained by Pavicic et al. Protein conformational changes caused by external RF/MW irradiation could trigger compensatory or adaptive cell response. The influence of applying an RF/MW of 864 MHz frequency radiation on fundamental biological processes had the likelihood of being active in the manner of biological stressors [66]. Later study demonstrated that RF-EMF exposure of human monocytes and lymphocytes by using different RF signals and exposure times did not have any activating capacity to induce reactive oxygen species (ROS) release or heat shock protein 70 (Hsp70) expression. Whereas, continuous and intermittent GSM-DTX exposure of human monocytes induced a significant decrease in ROS level during sham exposure, while human monocytes did not respond in the same manner [67].

The effect of EMF on human erythrocytes in vitro revealed that the amount of released hemoglobin increased with the time elapsed after the exposure to EMF both in the control and exposed erythrocytes; caused by increased membrane fragility. There were significant alterations in irradiated erythrocytes with hematocrit of 40% in a duration equal to or above 20 min, but none with hematocrit of only 20% for 60 min of EMF exposure. The effects of EMF radiation had a significant relationship with the position of human erythrocyte exposure [68]. The specific central nervous system (CNS) cells may activate different genes in response to cell phone emissions and there was variable threshold sensitivity depending on cell type. Short-term exposure to cell phone RF/MW radiation emissions could up-regulate specific intermediaries of apoptosis pathways in cells derived from the brain, and neurons that appeared to be more sensitive to this effect than astrocytes. Cell phone emissions have the potential to cause dysfunction or death through activation of specific intracellular cell death signaling pathways [69].

In contrast, some studies reported that there were no significant biological effects of EMF on human cells [70, 71, 72]. However, the duration of exposure and micronuclei, and total micronuclei frequency showed a positive correlation in initial year exposure, i.e. 0-1, 1-2, 2-3, 3-4 years. However, a slight decrease in the frequency of micronucleated cells and total micronuclei was observed for subjects exposed for more than 4 years[71]. The data on the biological effects of EMF on human cells in available literature are contradictory. Most probably because the experimental conditions were quite different for frequencies, intensity, exposure duration, positions, etc. More research and additional methods are necessary to resolve these contradictions and explain the mechanisms of RF EMF effects on health hazards.

2.5.2 Temperature change from exposure to RF

The study of van Leeuwen G.M.J. et al. [73] (1999) researched the change in brain temperatures due to exposure to a mobile phone in order to evaluate a realistic head model of the 3D temperature rise induced by such a device. This was done numerically with the consecutive use of an FDTD model to predict the absorbed electromagnetic power distribution, and a thermal model describing bioheat transfer both by conduction and blood flow. The authors calculated a maximum rise in brain temperature of 0.11 °C for an antenna with an average emitted power of 0.25 W, the maximum value in common mobile phones, and indefinite exposure. Maximum temperature rise was on the skin. The power distribution was characterized by a maximum averaged SAR over an arbitrarily shaped 10 g volume of approximately 1.6

Wkg^{-1}. Although this power distribution was not in compliance with all proposed safety standards, temperature rises were far too small to have lasting effects.

Wainwright P. [74] (2000) reported a study on the thermal effects of radiation from cellular telephones. A finite element thermal model of the head had been developed to calculate temperature rises generated in the brain by radiation from cellular telephones and similar electromagnetic devices**.** There were two sources of heat in the model: firstly, the natural metabolic heat production; and secondly, the power absorbed from the electromagnetic field. The SAR was derived from a finite difference time domain model of the head, coupled to a model `mobile phone', namely a quarter-wavelength antenna mounted on a metal box. The steady-state temperature distribution was calculated using the standard Pennes `bioheat equation'. In the normal cerebral cortex, the high blood perfusion rate served to provide an efficient cooling mechanism. In the case of equipment generally available to the public, the maximum temperature rise found in the brain was about 0.1 °C.

Gandhi O.P. et al. [75] (2001) reported the temperature rise for the human head for cellular telephones and peak SARs prescribed in safety guidelines**.** The bioheat equation was solved for an anatomically based model of the human head with a resolution of 3 × 3 × 3 mm to study the thermal implications of exposure to electromagnetic (EM) fields typical of cellular telephones both at 835 and 1,900 MH. Temperature increase, due to EM fields of cellular telephones, was fairly small and typically less than 0.1°C. Another objective was to study the thermal implications of the SAR limits for the occupational exposures of 8 W/kg for any 1 g; or 10 W/kg for any 10 g of tissue suggested in the commonly used safety guidelines. Such specific

absorption rates (SARs) would lead to temperature elevations for parts of the brain electromagnetically exposed up to 0.5°C with 10 W/kg for any 10 g of tissue, and larger volumes, resulting in somewhat higher temperatures. Similar temperature increases were also calculated by increasing the arterial blood temperature, except that temperature increases due to the SAR were for a more limited volume rather than the entire brain.

Bernardi P. et al. [76] (2001) demonstrated temperature elevation in the head of a cellular phone user in order to investigate the effect of SAR and contact with the phone. The maximum temperature elevations were obtained from the ear and brain of the user's head after 15 minutes of phone use. The results revealed that the mere contact of the cellular phone with the ear and cheek, even in a stand-by condition, in which no power was radiated and no power was internally dissipated, caused temperature elevations in the ear that reached 0.9 ^{o}C. The phone was initially at ambient temperature, which was usually lower than the ear temperature. Therefore, when the phone was put in contact with the ear, it determined a quick decrease in the ear temperature. Soon after, the heat supplied by blood and that coming from the neighboring tissues stopped this decrease, and the temperature started to elevate, going beyond the initial value, due to the suppressed convective exchange with air. Finally, when all heating effects were considered simultaneously, the maximum temperature elevation in the ear region was almost entirely due to the contact effect, with only a very slight contribution from SAR deposition. The situation, instead, was exactly opposite to that concerning the brain, in which the maximum temperature

elevation appeared to be mainly due to SAR, which, indeed, was able to heat up the head tissues more deeply than the contact effect.

2.5.3 Brain activity change from exposure to RF

A previous study also reported the effect of EMF on human brain physiology. Sixteen healthy young male subjects were exposed for 30 min to EMF of 900MHz (SAR 1W/Kg). The spectral power of EEG in non-rapid eye movement sleep was increased when compared to sham exposure [77]. Another study showed that under real exposure, EEG spectral power was influenced in some bins of the alpha band when compared to baseline and sham conditions. On EEG recording sessions, this effect was greater during EMF exposure than before it [78]. A recent study regarding the effect of EMF on human physiology demonstrated that spectral power of sleep EEG in non-REM sleep, stage 2 and slow wave sleep (SWS) had a dose-dependent increase in the slow and fast spindle frequency range after exposure to pulse-modulated RF EMF. There was a significant dose-dependent effect only in the fast spindle range. This evidence displayed that the influence of EMF exposure prior to sleep altered brain activity. This suggested a dose-response relationship between GSM exposure and its effects on the non-REM sleep EEG [79].

2.5.4 Effects of RF exposure on nervous systems

2.5.4.1 Effect on cell membrane

There was evidence that RF fields could affect membrane proteins and change the movement of ions across membranes. Some of these effects seemed to only occur in cells at temperatures well below normal body temperature or with RF intensities that caused significant heating. However, some evidence suggested that RF radiation at levels produced by mobile phones might influence ion channels and other membrane proteins of neurons in the brain under normal conditions. This might cause subtle changes in cell function, but the significance of such effects for human health was uncertain. Moreover, these effects had not been independently confirmed, which was important given the frequent lack of reproducibility of RF biological effects.

RF exposure had been reported to influence the ATP-dependent sodium/potassium pump in the membranes of human red blood cells, and this effect might also be mediated by membrane phase transitions [80, 81] (Allis and Sinha-Robinson, 1987; Liu et al, 1990). Effects on receptor proteins and their associated ion channels had also been described. For instance, Philippova et al [82] (1994) found that 900 MHz radiation, at SARs of 1 and 100 W/kg, specifically affected the binding of odorant molecules to the receptor protein in the membranes of olfactory receptor neurons in rats. Radiation at very low power densities could affect the ion channels associated with transmitter receptors: D'Inzeo et al [83] (1988) reported a decrease in the opening frequency of sodium channels associated with acetylcholine receptors in

muscle membranes, as a result of exposure to 9.75 GHz radiation at only 10–20 uW/m^2, which might cause a decrease in the excitability of the muscle.

2.5.4.2 Calcium efflux

Kittel et al [84] (1996), using electron microscopy to identify labelled calcium in a particular part of the brain (the medial habenular nucleus), found that exposure of mice in vivo to 2.45 GHz RF fields, amplitude modulated at 16 Hz, caused a reduction in the number of calcium-containing vesicles inside nerve cells and an increase in the amount of calcium precipitated on the surface of the cells. However, calcium efflux from brain explants almost certainly involves a number of other factors, including the release of calcium bound or adherent to membranes and simply trapped in the interstices of the tissue. It is also likely to be influenced by temperature.

Adey [85, 86] (1989, 1993) suggested that changes in calcium efflux may be due to an amplification process, in which weak electric fields might be set up in the tissue at an extremely low frequency of amplitude modulation, possibly acting as a “trigger” for the initiation of long-range co-operative events within the cell membrane. However, there was no obvious theoretical basis for such effects, which would seem to require the presence of a non-linear mechanism operating on the timescale of the carrier frequency. This was not the case for ion-gating mechanisms.

2.5.4.3 Neurotransmitter systems

Modak et al. [87] (1981) reported that RF exposure caused a decrease in the concentration of important transmitter acetylcholine in the mouse brain, but they employed a very intense 2.45 GHz single pulse, causing a 2–4 ^{oC} rise in temperature. The rate-limiting step in the synthesis of acetylcholine is the uptake of choline by nerve cells. Dutta et al. [88] (1992) detected an increase in the activity of the enzyme, acetylcholinesterase, (which hydrolyses acetylcholine) in cultured human neuroblastoma cells exposed to low intensity RF fields, and amplitude modulated at 16 Hz.

In an extensive series of experiments, Lai and colleagues [58, 89-93] (Lai et al, 1987, 1989a,b, 1990, 1991, 1994) reported that 20 minutes exposure of rats to pulsed 2.45 GHz radiation at low intensities caused an increase in choline uptake and a reduction in the concentration of acetylcholine receptors, whereas exposure for 45 minutes had the opposite effect. Pretreatment of animals with naltrexone (which blocked opioid receptors) or corticotrophin-releasing hormone was found to prevent these effects. Although the average intensities used in these studies were relatively low, the findings might depend on thermal effects, especially since acetylcholine was known to be involved in transmission in the parts of the hypothalamus responsible for temperature regulation, which was acutely sensitive to temperature change.

2.5.5 Symptoms associated with mobile phone use

Some studies reported the relationship between headache and mobile phone use. A preliminary study by Hocking B. reported symptoms associated with mobile phone use. That study recruited respondents from a notice in a medical journal in 1996. Its aim was to survey the natural characteristics of symptoms occurring from mobile phone use as an aid to further research. Respondents contacted the writer and were subsequently interviewed at length by telephone with the aid of questionnaires. These questionnaires were developed by international collaborators in the UK and Sweden. The results showed that there were 50 initial respondents, of whom 40 (80%) were subsequently contacted for an interview. Seventy-five percent were male and aged between 30 and 49 years. They lived in Queensland, New South Wales, Victoria, South Australia and Western Australia. The symptoms arising from mobile phone use mainly involved headache. The most common site was the temporal area in 17(48%) respondents and the occipital area in 9(26%). The pain radiated to the jaw, neck, shoulder or arm in a few cases. The majority of 23(65%) respondents felt a sensation in less than 5 minutes after commencing the mobile phone call, but another 12(35%) felt the sensation building up as the day progressed. Sixteen (46%) suffered every time they used the mobile phone. The duration of calls was considered to be an influence on symptoms in 30(75%) respondents, and associated with digital mobile phone use. No respondents had symptoms when using an ordinary telephone handset. Two cases were diagnosed as migraine, and 1 used an analogue phone without symptoms, but another developed symptoms with digital phone use and was diagnosed as having migraine. Eleven cases (31%) revealed some transient effects on

their vision including blurring, and 15(43%) cases reported other symptoms such as nausea, dizziness or fuzziness. Most of the respondents obtained relief by altering their patterns of telephone usage or type of phone [23].

In 2000, Chia et al. carried out a cross-sectional community study in Singapore to determine the prevalence of specific symptoms of the central nervous system (CNS) among handheld cellular telephone (HP) users and compared it to nonusers. They also studied the association of risk factors and CNS symptoms among HP users. Eight hundred and eight men and women aged between 12 and 70 years were selected by using one-stage cluster random sampling, and they responded to a structured questionnaire. The results showed that the prevalence of HP users was 44.8%, and headaches were more common among users of hand-held mobile phones than in non-users (65% vs 54%), with an RR: 1.31 (95%CI: 1.00-1.70). Headache prevalence increased with duration of use, and the use of hand-free equipment reduced the increase by more than 20%. Even so, the use of HPs was not associated with a significant increase of CNS symptoms, other than headache [29].

Later, in 2001, Sandström et al. conducted a cross-sectional and epidemiological study of digital system (GSM) and analogue system (NMT) 900 users, which was based on a questionnaire completed by mobile phone (MP) users in Sweden and Norway. That study focused on the possible health effects caused by microwaves emitted to MP users. There were 6,379 GSM users and 5,613 NMT 900 users in Sweden, and 2,500 from each category in Norway. The results revealed that headaches and other symptoms were higher in users of analog (NMT 900) phones than in users of digital (GSM) ones. However, secondary findings revealed a

significant association between the time/number of calls per day and the prevalence of warmth behind/around or on the ear, headaches and fatigue [94].

In another study at King's College London, Rubin et al. conducted a double blind, randomized test within a participants' provocation study between September 2003 and June 2005. The goal of this study was to test the association of headache severity with sensitive mobile phone signals among people who had symptoms when exposed to a pulsing mobile signal and sham or non-pulsing signal. Sixty people reported frequent headache while using a global system of mobile communication (GSM) and 60 controlled participants did not report any symptoms. Participants were exposed to three conditions: a 900 MHz GSM mobile phone signal, a non-pulsing carrier wave signal, and a sham condition with no signal present. Each exposure lasted for 50 minutes. The results showed that Headache severity increased during exposure and decreased immediately afterwards, but there was no significant difference between the conditions in terms of symptom severity in either group. The proportion of sensitive participants during GSM exposure (60%) was similar to that for sham exposure (63%) [95].

A cross-sectional epidemiological study among 17,000 people in Norway and Sweden was carried out by Oftedal et al. [96] in 2000. The results indicated that headache typically manifested during or within 30 minutes after a call and most people's symptoms continued for up to 2 or 6 hours after the call. However, in some cases the headache lasted for more than 6 hours. Nearly 40% of headaches experienced had symptoms ipsilaterally relative to the side where the mobile phone was held. Those symptoms comprised sensations of warmth on or behind/around the

ear, burning sensations on facial skin and headaches, and they were most commonly connected to mobile phone use, with a significant probability of headache and burning skin. Interestingly, in both countries, about 45% of the people with symptoms attributed to mobile phone use had taken steps to reduce the symptoms, including decreasing calling time and using hand-free equipment. Most of the people experienced that taking these steps led to a reduction of symptoms.

Abdel-Rassoul G. et al. [97] (2007) carried out a cross-sectional study on neurobehavioral effects among inhabitants around mobile phone base stations, and the results showed that the prevalence of neuropsychiatric complaints, consisting of headache, memory changes, dizziness, tremors, depressive symptoms, and sleep disturbance, were significantly higher among exposed inhabitants than in controls. A recent double blind, sham-controlled provocation study [33] was the same in that no indication of radiofrequency (RF) exposure was found causing pain or discomfort in the head, or any other symptoms, in GSM 900 MHz users. This lack of effect was seen both in subjects attributing symptoms to mobile phones and among controls. Eltiti et al. [98] investigated the effect of electric and magnetic fields in a provocation study by conducting both open and double-blind tests. The results exhibited that the sham exposures caused significantly fewer symptoms than real exposure conditions, but not in the double-blind tests.

Moreover, Szyjknowska A. et al. [99] (2005) conducted a survey study using a self-reported questionnaire. The findings demonstrated that 70% of respondents complained of headache and 20% of dizziness. Impaired concentration occurred in 56% of respondents and facial dermatitis was reported by 11%. The most prevalent

symptom related to mobile phone use was the thermal sensation within the auricle and behind/around the ear. In reports on symptoms and health, no respondents complained about the medical check-up or medication.

2.5.6 Reduction in exposure to RF by using hands-free accessories

The initial research of biomedical engineering was performed in order to find out the reduction of non-thermal effects on the brain, due to a new device used for mobile telephones. This new Neutralising Protective Device (NPD) is a sticker placed on the back of the actual mobile telephone case, as close as possible to the antenna. This device is passive in the presence of natural radiation and surrounding objects, but becomes active in the presence of radiation from mobile telephones, and does not affect the quality of the mobile's efficiency. An electroencephalograph (EEG) was recorded while the respondents' eyes were open at the base-line, and these records were compared with those from the NPD by use of the mobile telephone with and without one of the devices for each five minute period. The results realized that the percentage distribution of brain frequencies with the NPD tended to be the same as the initial basal state of the subject at the start of the experiment. When the subjects were listening without the NPD, a significant variation in the percentage of brain rhythms was observed. These findings suggested that the NPD reduced the non-thermal effects on the brain, as results showed that the EEG changes tended to return to their recorded basal condition [100].

In another study, Bit-Babik et al. [30] (2003) demonstrated a significant impact of RF energy coupled into the leads of hands-free accessories, and this was strongly

attenuated by the body. Numerical simulations using the Finite-Difference Time-Domain (FDTD) method and experimental measurements with a miniature electric-field probe were in good agreement and showed a decrease, not an increase, in RF energy exposure in the human head from hands-free accessories. SAR to the user's head was substantially reduced by the use of a wired ''hands free'' earphone-microphone extension. In a previous study by Chou et al. [31] (2001), the results from appropriate tests showed that these "hands-free kits" were effective in reducing RF to the head (although if the handset was worn near the body, they may increase exposure to other parts of the body). In addition, such devices did not require a user to hold the handset during use, so this also added convenience.

In an experimental study of test conditions used for SAR tests of hands-free kits [101], the results showed that the expanded uncertainty in SAR values was 40% for absolute measurements. For comparative measurements, as described in that report, many of the contributory uncertainties equally affected paired comparative measurements, and uncertainties were reduced to approximately 5%. Exposure from personal hands-free (PHF) kits was raised when the earpiece cable was placed in contact with the cheek of the phantom. This gave generally higher SAR values for PHF kits than when the earpiece cable hung vertically downwards, although the maximum exposure occurred in the cheek rather than at the ear/brain location.

In that study, the inclusion of recent-model phones with internal antennas showed lower RF signal levels close to the phone on the keypad side, which could lead to low SAR. With a PHF, however, SAR levels were similar to those obtained with external antenna phones, and there was little or no reduction in 'worst-case' SAR

in the head from internal antenna phones using PHF kits. Nevertheless, the hand probably received higher exposure than the head during the normal use of an internal antenna phone [101].

With a PHF kit in use, the maximum body absorption depended on where the mobile phone was placed. If it was in the hand, the situation was similar to normal use of the phone against the ear. If it was in a pocket, then the body absorption was expected to depend on which way round the phone was placed. There would be lower body dose by ensuring that the keypad of the phone was facing the body. The hand acted as an absorber reducing the SAR to the head from the PHF. Other parts of the body would behave similarly depending upon where the phone was deployed. The measurements made with a ferrite absorber attached to the cable showed that there was plenty of design scope in reducing RF emissions from the cables and making PHF kits with even lower 'worst-case' SAR levels. Even so, no significant differences in performance between the various models of PHF cable tested had become apparent. In conclusion, in their intended mode of use, personal hands free kits offered very substantial reductions in SAR compared to the normal use of a mobile phone held against the ear. If ferrite suppressers were added to the earpiece cables, then even lower levels of exposure could be achieved [101].

The findings from the experimental studies [30, 31, 101] above supported some cross-sectional and epidemiological studies [29, 96] showing the related symptoms from mobile phone use, however, those symptoms were reported to reduce after personal hands-free kits were used as substitutable material with a mobile phone.

In the first half of the year 2000, various publications appeared concerning a possible increase in SAR through the use of headsets. With the aid of a headset connected to a mobile telephone (a cable with a microphone and small loudspeaker worn in the ear) it was possible to make calls without holding the telephone against the ear. Many studies had been conducted in various laboratories. Those studies confirmed the theoretical analysis of a mobile telephone in combination with a headset. In addition, it was concluded that the use of a headset generally reduces SAR substantially and under no circumstances leads to SAR in the head, which was higher than or similar to that from the use of a mobile telephone without a headset [102].

2.5.7 Other precipitating factors for migraine headache

Many previous studies described the trigger factors associated with migraine headache. A recent study conducted a systemic review to determine the role of hormones on menstrual migraine between January 1966 and September 2005 from search articles already published in the English language. A total of 643 unique articles were reviewed. Results showed that the influence of estrogen made the prevalence of migraine higher among women than men by 3 times, and there was a significant change in migraine incidence in female reproductive status. Menstrual migraines were usually more resistant to treatment and associated with more functional disability compared with attacks at other times of the month [9]. Siniatchkin et al. (2006) also reported that Migraineurs had a significant amplitude increase of the initial contingent negative variation (CNV) component in the premenstrual phase compared with ovulation. During both the ovulation and premenstrual phases both Migraineurs and controls demonstrated a significant increase of the CNV amplitude

on stress. However, the increase of the amplitude on stress in the premenstrual phase was more pronounced in Migraineurs [10].

In another study, Martin et al. (2006) conducted a randomized-controlled trial in order to determine the association between severity of premenstrual symptoms (PMS) and headache outcome measurements during natural menstrual cycles and after medical oophorectomy. Twenty-one participants were obtained. The menstrual cycle dataset was composed of data from three natural menstrual cycles. Each menstrual cycle was subdivided into seven 3-day intervals based on urine hormone metabolites. The medical oophorectomy dataset included data from a 2-month treatment period in which a medical oophorectomy was included by gonadotropin-releasing hormone agonists (GnRHa). Participants were randomized to transdermal estradiol or a matching placebo. The results revealed that the PMS index significantly correlated with the headache index during native menstrual cycles ($r=0.47$, $p<.05$) and during all seven intervals of the menstrual cycle, respectively [11]. Kibler et al. (2005) carried out a prospective study to examine correlations between hormone levels and migraine frequency, severity, and migraine-related disability. It was found that the migraine group evidenced lower premenstrual luteinizing hormone and more menstrual distress symptoms at each phase of the menstrual cycle. Hormones were associated with migraine activity and disability within cycle phases and across phases in a time-lagged manner. Menstrual distress was associated with ovulatory phase migraine activity and with migraine-related disability across the menstrual cycle. In summary, both reproductive hormones and menstrually related distress appear to predict migraine at each phase of the menstrual cycle [12]. Demarquary et al. (2006)

conducted an experimental study to evaluate olfactory hypersensitivity (OHS) between attacks in migraine patients. Seventy-four migraine patients and 30 controls were enrolled from November 2001 to June 2003. The presence of OHS was evaluated using an oral questionnaire and a chemical odour intolerance index. Subjects had to rate the intensity and hedonicity of 12 odourants using a linear rating scale. It was found that migraine patients only reported an interictal OHS of about 35.2%, but there were no controls present. Patients with OHS presented a greater attack frequency, higher number of dour-induced migraines and visual hypersensitivity when compared with other patients. OHS Migraineurs judged odours less pleasant than other patients and controls did. However, OHS between attacks was significantly associated with odour-triggered migraine and an alteration of hedonic judgment [13].

Martin et al. (2005) also carried out an experimental study to find out the causal relationship between negative affect (NA) and headache, and noise (N) and headache. Twenty-four Migraineurs and 44 subjects with tension–type headache were randomly assigned to one of four experimental conditions defined by the presence or absence of two antecedent challenges, and a stressor (S) designed to induce NA and N. Laboratory sessions were divided into adaptation, baseline, challenge, and recovery phases. Responses were measures in terms of headache intensity ratings, forehead electromyographic activity, heart rate, blood pressure, and temporal pulse amplitude (TPA). The results showed that both NA and N precipitated headache. These factors did not interact in triggering headache. Furthermore, headache induced

by N were associated with elevated TPA, but headaches induced by NA were not associated with significant physiological changes [14].

Karli et al. (2005) reported their study on the trigger factors of the preheadache phases of episodic tension-type headache (ETTH), typical aura with non-headache (TANMH), migraine with (MA) and without aura (MwA). The aim of their study was to investigate the preheadache phases and trigger factors of these headache types based on questionnaires. A total of 96 patients including 31 ETTH, 9 TANMH, 23 MA and 33 MwA patients were recruited in the study. It was found that only two groups and five individual trigger factors were significantly different between groups. Hunger and dour were significantly more common in MA, MwA and TANMH patients. Food was a significant precipitant factor for headache only in MA patients [15].

Zivadinov et al. (2003) performed a population-based survey using a "face-to-face door-to-door" interview method. The purpose of their study was to estimate the prevalence of tension-type headache (TTH) and establish the frequency of precipitating factors in subjects with migraine and TTH, and migraine subtypes: migraine with (MA) and without aura (MO). The surveyed population consisted of 5,173 residents aged between 15 and 65 years, of which 3,794 (73.3%) had a headache history according to the International Headache Society (IHS) criteria. Headache screen-positive responders of about 2,475(65.2%) were interviewed with structural questionnaires. The results showed that the most common precipitants for both migraine and TTH were stress and frequent traveling. Stress was associated with migraine (OR: 1.4, 95%CI: 1.17-1.69), whereas physical activity was related to

TTH(OR: 0.72, 95%CI: 0.58-0.87). Frequent traveling, food items, and changes in weather conditions and temperature exhibited a significantly positive association with MA. Lifetime Migraineurs experienced headache attacks preceded by triggering factors more frequently than TTH. MA was more frequently associated with precipitating factors than MO [18].

Wacogne et al. (2003) conducted a study in the Cephalalgia and Migraine Centre of Laennec Hospital (Paris). The studied population consisted of Migraineurs matched to IHS criteria who were visiting the centre for the first time, and a control group of non-migraineurs. The controls were healthy volunteers matched for age and sex, and working in Laennec Hospital. The aim of the study was to evaluate the stress level and intensity of anxiety and depression disorders in migraine patients compared with the control group of healthy workers, based on questionnaires. It was found that stress and anxiety were higher in the migraine group than in the control group and above the clinical level. Depression scores remained low in both groups. Stress was a primordial factor in the triggering and perpetuation of migraine attacks. It may be necessary to manage stress in order to improve the daily life of Migraineurs [21].

Spierings et al. (2001) reported their study of precipitating and aggravating factors for migraine versus tension-type headache. The goal of this study was to determine whether there were precipitating and aggravating factors of headache that differentiate migraine from tension-type headache. There were 38 Migraineurs and 17 patients with tension-type headache. They were enrolled and interviewed by telephone using a questionnaire. The results revealed that the most common precipitating factors in both groups of patients were stress/tension, not eating on time,

fatigue, and lack of sleep. Weather, smell, smoke, and light were the precipitating factors that differentiated migraine from tension headache [19].

Chabriate et al. (1999) carried out a prospective study of precipitating factors in migraine patients. Three hundred eighty-five Migraineurs and 313 non-migraineurs were recruited in their study. The most frequent precipitating factors in both groups were fatigue, and/or sleep, stress, food and/or drinks, menstruation, hot/cold weather, and infections. All these factors except infections were reported to cause headache more frequently in Migraineurs than in non-migraineurs. Mean intensity of headache related to fatigue and/or sleep, stress, food and/or drinks, hot/cold weather, and menstruation varied from 37 to 43 in Migraineurs and 29 to 35 in non-migraineurs. These results supported that endogenous factors were the most frequent triggers of headache in migraineurs [20].

In thoroughly reviewing the literature, it was important for treatment to know the trigger factors that could aggravate or precipitate migraine in the individual patients who developed more frequent attacks of headache. One program of migraine treatment helped patients to avoid the trigger factors in order to decrease frequent episodic headache and its severity in order to improve their quality of life. There were many experimental studies to find out the biological effects from radiofrequency exposure. Some observational studies reported the related symptoms from mobile phone exposure, especially the headache symptom. However, it was not clear whether the effect of mobile phone exposure in migraine patients could cause or aggravate migraine severity or not. Hence, this study was conducted to test the hypothesis that hands-free kits could reduce RF exposure when used with a mobile phone directly.

Therefore, case definitions of mobile phone and non mobile phone exposure to RF were carried out within the research methodology of this study.