

A theoretical model based upon mast cells and histamine to explain the recently proclaimed sensitivity to electric and/or magnetic fields in humans

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Summary The relationship between exposure to electromagnetic fields (EMFs) and human health is more and more in focus. This is mainly because of the rapid increasing use of such EMFs within our modern society. Exposure to EMFs has been linked to different cancer forms, e.g. leukemia, brain tumors, neurological diseases, such as Alzheimer's disease, asthma and allergy, and recently to the phenomena of 'electrosensitivity' and 'screen dermatitis'. There is an increasing number of reports about cutaneous problems as well as symptoms from internal organs, such as the heart, in people exposed to video display terminals (VDTs). These people suffer from subjective and objective skin and mucosa-related symptoms, such as itch, heat sensation, pain, erythema, papules and pustules. In severe cases, people can not, for instance, use VDTs or artificial light at all, or be close to mobile telephones. Mast cells (MCs), when activated, release a spectrum of mediators, among them histamine, which is involved in a variety of biological effects with clinical relevance, e.g. allergic hypersensitivity, itch, edema, local erythema and many types of dermatoses. From the results of recent studies, it is clear that EMFs affect the MC, and also the dendritic cell, population and may degranulate these cells. The release of inflammatory substances, such as histamine, from MCs in the skin results in a local erythema, edema and sensation of itch and pain, and the release of somatostatin from the dendritic cells may give rise to subjective sensations of on-going inflammation and sensitivity to ordinary light. These are, as mentioned, the common symptoms reported from patients suffering from 'electrosensitivity'/'screen dermatitis'. MCs are also present in the heart tissue and their localization is of particular relevance to their function. Data from studies made on interactions of EMFs with the cardiac function have demonstrated that highly interesting changes are present in the heart after exposure to EMFs. One could speculate that the cardiac MCs are responsible for these changes due to degranulation after exposure to EMFs. However, it is still not known how, and through which mechanisms, all these different cells are affected by EMFs. In this article, we present a theoretical model, based upon observations on EMFs and their cellular effects, to explain the proclaimed sensitivity to electric and/or magnetic fields in humans. © 2000 Harcourt Publishers Ltd

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INTRODUCTION

Today living systems, and among them especially humans, are widely exposed to a whole variety of man-made electromagnetic fields (EMFs) in all aspects of modern life to a degree never experienced before on this

planet, most of it resulting from technological advances over the past 40 years. Whether at home or at work, EMFs generated by domestic wiring, overhead high-voltage power lines and occupational equipment, as well as other environmental sources such as radar, microwave communications systems, radio and television broadcasting, cellular telephones, and the ubiquitous visual display terminals (VDTs), all contribute to an individual's more or less chronic exposure.

An increasing number of people are claiming that they are hypersensitive to electricity. These patients suffer from cutaneous as well as neurological symptoms when they are near electrical equipment, including VDTs, fluorescent light (especially high-frequency ones), mobile telephones, television or other electrical appliances. The most common complaints are headache, eye and general fatigue, and sensory symptoms such as itching, stinging, pain or burning sensations in the skin (1,2). The patients may also have objective, visible symptoms such as erythema, papules and pustules. Some patients also have symptoms from internal organ systems, such as the heart and the central nervous system. Other symptoms may be breathing problems, stuffy or runny nose and sinus problems (1). At first, the symptoms have an intermittent character and disappear at short-term rest away from the source of the electricity, but for some patients the symptoms become more persistent. In severe cases, people can not, for instance, use VDTs or artificial light at all (2). Based on these clinical symptoms and their attribution, we have named these patients categories 'screen dermatitis' (mainly meaning persons with skin problems in front of VDTs) and 'electrosupersensitivity' (meaning persons with a more general symptomatology and attribution).

Cutaneous changes in 'screen dermatitis' patients was early observed by Björn Lagerholm, a Swedish dermatologist at the Karolinska Hospital in Stockholm. His data, however, have not, unfortunately, been fully published or acknowledged.

Johansson et al. (3) and Johansson and Liu (1) showed, in their studies on effects of exposure to VDTs and possible changes in the skin, that certain profound changes in the dermis and epidermis take place after such an exposure. They also observed skin changes in patients claiming to suffer from 'screen dermatitis', before provocation, as compared to normal healthy controls (1,3,4).

In our previous paper (5), we compared the skin damages due to UV-light and ionizing radiation, including X-rays, with the cutaneous manifestations seen in 'screen dermatitis' in order to elucidate possible similarities and/or differences. Our results demonstrated that highly similar changes exist in the skin of 'screen dermatitis' patients, as regards the clinical manifestations as well as alterations in the cell populations, including mast cells (MCs), and in skin damaged by UV-light/ionizing radiation.

In 'screen dermatitis/electrosupersensitivity' patients a much higher number of MCs have been observed, as compared to healthy controls (1,3,6), and the cytoplasmic granules, in the patient group, were found to be more densely distributed and more strongly stained. Furthermore, the size of the infiltrating MCs was found to be larger in the patient group as well. The high number of MCs and the possible release of specific substances, such as histamine, may explain these patients' clinical symptoms of itch, pain, edema and erythema. Recently, highly relevant changes in RBL-2H3 cells, a MC analogue, after exposure to electromagnetic radiation have also been observed by Donnellan et al. (7).

It is very plausible that changes are present in MCs in patients claiming to suffer from 'electrosupersensitivity'/'screen dermatitis' after exposure to EMFs. So far, however, it is not known how, and through which mechanisms, EMFs could affect the MCs and their release of inflammatory mediators. In the present paper, we would thus like to speculate about such possible mechanisms for EMFs to affect the MCs and their release of specific substances. Initially, regarding the cellular and molecular details for such a model, we give a detailed background, followed by a description of the relevant data from studies of effects of EMFs. Finally, a model is presented based upon these observations.

MATERIAL AND METHODS

Literature from 1937 until 1998 concerning mast cells, histamine and electromagnetic fields, as well as cutaneous manifestations seen in 'screen dermatitis' or 'electrosupersensitivity' was selected. All literature studied is found in the reference list.

RESULTS AND DISCUSSION

The mast cell

The MC is a characteristic granular tissue cell that can be found especially along the epithelial linings of the body facing the external environment, such as the skin, and the respiratory and gastrointestinal tracts, adjacent to blood or lymphatic vessels, and near or within peripheral nerves (8,9). The MC's distribution makes its cell products available to fibroblasts and other cells of the connective tissue, surface or glandular epithelial cells, nerves, vascular endothelial cells, and vascular, respiratory, gastrointestinal, or genito-urinary smooth muscle cells.

MCs are known to be involved in a variety of physiological and pathological conditions, such as immediate hypersensitivity (10), delayed hypersensitivity (11,12), cell growth regulation (13,14), neoplasia defense (15), and the sensation of pain and itch (16).

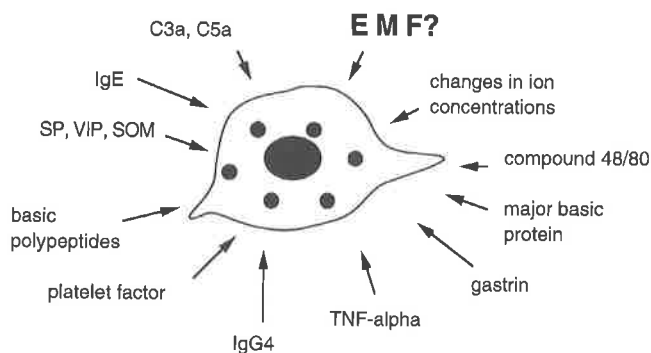


Fig. 1 Agents capable of activating mast cells (MCs) leading to mediator secretion, and possible interactions from changes in ion concentrations and electromagnetic fields (EMFs) (further dealt with in Fig. 2). Mast cells may be activated by a plethora of chemical agents which leads to degranulation and release of MC inflammatory mediators, including histamine. Some of these agents, such as specific antigens and anti-IgE, activate these cells by cross-linkage of cell surface IgE, and mimic the mechanism whereby MCs respond to allergens during the acute allergic reaction. However, other agents act independently of IgE-receptors. Included in this group are a variety of polybasic compounds, e.g. compound 48/80, and neuropeptides such as substance P (SP), vasoactive intestinal polypeptide (VIP) and somatostatin (SOM). Several other agents known to cause MC degranulation are the complement-derived anaphylatoxins C3a and C5a (92), platelet factor, IgG₄ and some cytokines, such as tumour necrosis factor- α (TNF- α) and interleukin-1 (IL-1). Gastrin has also been reported to activate histamine release from adult human skin slices *in vitro* (93).

Mammalian MCs contain a large number of mediators. In addition to histamine (17), they contain heparin (18,19), hyaluronic acid (20), melanin (21), serotonin (22), dopamine (23) and vasoactive intestinal polypeptide (VIP) (24).

Human MCs can be divided into two major subtypes: MC_T cells that contain only tryptase and MC_{TC} cells which contain tryptase, chymase, carboxypeptidase and a cathepsin G-like proteinase (25–29). In normal skin and the intestinal submucosa MCs are mainly of the MC_{TC} type (25–27,30,31), while the majority of the MCs of the lung and the intestinal mucosa are of the MC_T type (25–27,30).

MCs can be activated in different ways (Fig. 1). The cross-linkage of immunoglobulin E (IgE) molecules and their high-affinity receptors by an allergen leads to degranulation and release of MC inflammatory mediators, such as histamine. Also, the neuropeptides substance P (SP), VIP and somatostatin (32–34), as well as the anaphylatoxins C3a and C5a of the complement system and a human neutrophil-derived histamine-releasing activity (HRA-N) (35), can release histamine from these cells. The release of MC mediators may also be a response to a change in ion concentration with edema (*spongiosis*) (36). Furthermore, MC degranulation is also induced by

some cytokines, such as tumour necrosis factor- α (TNF- α) (37) and interleukin-1 (IL-1) (38). On the other hand, MCs which stain positively for IL-4 (39,40), but not for interferon- γ (IFN- γ), have recently been shown to be increased in the lesional skin of atopic dermatitis patients, which indicates a close linkage between MCs and the immune system (41). There is a great difference in the secretory response to IgE-dependent and IgE-independent stimuli. The latter cause a much more rapid release of histamine and are relatively independent of extracellular calcium (42).

Histamine

Histamine is involved in a variety of biological effects with clinical relevance, e.g. allergic hypersensitivity, gastric secretion, asthma, itch, and many types of dermatoses. Histamine, on reaching the extracellular environment, produces its physiological effects by stimulating specific cell surface receptors designated H₁ and H₂. A wide variety of pharmacological effects are produced which includes increased vascular permeability, vasodilatation and contraction of airways and visceral smooth muscle. All of these effects are mediated through stimulation of H₁-receptors. Stimulation of H₂-receptors results in increased gastric acid secretion by parietal cells, inhibition of mediator release from basophils, neutrophils and lymphocytes, and augmentation of T cell suppressor activity.

An intradermal administration of histamine into human skin results in a local erythema, edema and often also the sensation of itch and/or pain. Only the edema and itching reactions are considered to be directly caused by histamine released from MCs, whereas the flare is attributed to the release of SP and/or calcitonin gene-related peptide (CGRP) from the surrounding nerve terminals (cf. Ref. 43).

The major bodily location of histamine in mammals are the MCs (17). Histamine is synthesized in MCs from histidine and is stored within the MC secretory granule by forming a complex with the glycosaminoglycan side chains of heparin. The association between these two mediators, however, is loose, and upon MC degranulation histamine rapidly leaves the granule by cation exchange with extracellular sodium ions (44).

But histamine has also been found in basophils, in some endocrine cells of the intestinal mucosa (45) and more recently in some nerve cell populations of the central nervous system (46–48). There are also some reports of histamine located in other cell types and tissues, among others the epidermis of skin (49) and the capillary endothelium (50). Johansson et al. (51) have recently reported the presence of histamine-immunoreactive nerves in the skin of Sprague–Dawley rats using a new

and highly sensitive immunohistochemical approach (52,53).

Mast cells in allergy and asthma

The allergic inflammatory response that occurs in individuals with asthma, allergic rhinitis, or atopic dermatitis, is characterized by the presence of MCs, as well as other cell types, such as basophils, eosinophils, monocytes, T cells, and B cells (54). Allergic reactions often begin with an immediate-phase response, due to MC degranulation, typically lasting 20–30 minutes. On antigen challenge, the immediate-phase response is followed 4–6 hours later by a late-phase reaction, with more profound tissue swelling, accompanied by an influx of inflammatory cells causing symptoms such as bronchospasm and nasal congestion. MC degranulation during the immediate-phase response initiates an increase in vascular permeability but, more importantly, initiates the expression by vascular endothelial cells of specific adhesion molecules such as VCAM-1 or secretion of chemokines such as RANTES and ectoxins (55). This results in the selective recruitment of eosinophils, monocytes, and T and B lymphocytes (56,57), which amplify and prolong the allergic inflammatory response.

Mast cells and neuropeptides

Human skin MCs respond to neuropeptide stimulation with a rapid release of histamine (32,33).

Normal human skin has many neuropeptides: SP, neurokinin A (NKA), somatostatin, VIP, peptide histidine isoleucine (PHI) and peptide histidine methionine (PHM), CGRP, neurotensin, neuropeptide tyrosine (NPY), atrial natriuretic peptide, galanin and γ -melanocyte stimulating hormone (58–64). For a recent review, see Rossi and Johansson (65).

SP is present in small-diameter primary afferents that belong to the C-fiber group. SP is one of the most potent vasodilators known and could be an important mediator of antidromic vasodilatation, an effect that correlates well with the putative role of SP in pain transmission (66–68). SP also increases both vasodilatation and vascular permeability (69).

SP receptors have been demonstrated on MCs, polymorphonuclear leucocytes, and macrophages (70,71). An intradermal injection of SP in normal skin causes pronounced inflammatory changes at picomolar concentration (72), including an erythematous reaction in the surrounding skin. This reaction fades in approximately 45 to 60 seconds and is replaced by a more persistent darker erythema with an outline that does not coincide with that of the early erythema and lasts for up to 2 hours. It also induces weal formation with a dose-related mean

diameter (SP is about 100 times more potent on a molar basis than histamine). The cutaneous erythema and edema, after the intradermal injection of SP, is provoked by two different mechanisms: one caused by MC histamine release and another independent of histamine release (64,73).

Actions of VIP on the skin include pruritus, weal and flare responses (74). These effects are inhibited by pyrilamine, indicating that the response to VIP is mediated by histamine, and furthermore, MCs can release VIP by histamine liberators (24).

Direct effects of EMFs on mast cells

As mentioned before, epidermal MCs may release inflammatory mediators in response to a change in ion concentrations (36). In a study by Gorczynska and Wegrzynowicz (75), the magnetic field influence on the concentration of serum potassium, sodium and chloride was tested in guinea-pigs. It was shown that a static magnetic field induction of 0.3 mT–5 mT produced progressively an increase in the sodium concentration and a decrease in the chloride concentration of the serum. No change in potassium serum concentration was observed following magnetic field exposure. They also showed that the range of observed changes was dependent on the duration of exposure to the magnetic field. From this observation one can speculate that MC degranulation could occur in resonance to changes in ion concentrations initially due to exposure to magnetic fields.

Activation of MCs and basophils by binding of ligands that cross-link and micro-aggregate cell surface receptors leads to a series of responses, including a phosphoinositide cascade, elevation of intracellular free calcium, morphological changes in the cell plasma membrane, and ultimately, exocytosis of granules containing histamine and other mediators of the allergic response (cf. Ref. 32). Feder and Webb (76) showed in a study on rat basophilic leukemia (RBL) cells, a tumor MC line, that receptor motion and aggregation is induced by application of small (10 V/cm) static electric fields. They also observed a sustained rise in intracellular free calcium in RBL cells induced by the application of such small static electric fields. However, their experiments suggested that the rise in intracellular free calcium is not due to a direct membrane perturbation, such as electroporation, nor did it resemble the effects observed upon antigenic cross-linking; therefore they concluded that the molecular mechanisms inducing this second messenger signal are distinct from the response to an antigen. Furthermore, Feder and Webb (76) proposed that redistribution of membrane constituents, to activate a physiological response, compromise a general mechanism for interaction of small electric fields with cellular systems!

In a study on the effects of constant magnetic fields of low energies (35 mT) on mesenteric MCs, active reactions of these cells to the magnetic fields was observed (77), and a high lability of the cellular system was demonstrated.

In experiments with albino rats subjected to whole-body pulsed electromagnetic irradiation of 100 mT magnetic induction (78), significant changes were revealed not only in the content of all studied bioamines (catecholamines, serotonin and histamine) of the spinal ganglia, but in the histamine/serotonin ratio as well.

Furthermore, Iurina et al. (79) studied the effects of single and repeated exposure of mice, rats, and rabbits to magnetic fields at 50 Hz and 2 kA/m, 16 kA/m, or 32 kA/m on the population of dermal, intestinal, and popliteal lymph node MCs, immediately and within one month after exposure. They observed that repeated exposure for 4 hours during 5 days modulated the functional activity of MCs in all the organs. More extended (1.5–2 months) repeated exposure to the most intensive (=32 kA/m) magnetic field stimulated adaptation and regain of the MC populations in the dermal and popliteal lymph nodes, whereas enhanced degranulation of MCs persisted in the intestine. Iurina et al. (79) suggested that the high magnetic sensitivity of MCs revealed in their study could be used as a test of body reactivity and adaptation to this physical agent!

Finally, there are also reports indicating tissue-specific effects (80) as well as the appearance of EMF-modulating effects on the number of mast cells in healing skin (81). However, also single studies finding a lack of such biophysical correlations are found in the literature (see e.g. Ref. 82).

Cardiac mast cells

MCs are present in normal, and even more abundant in diseased, human heart tissue and their localization is of particular relevance to their function. Within heart tissue, MCs lie between myocytes and in close contact with blood vessels. They are also found in the coronary adventitia and in the shoulder regions of a coronary atheroma (83). Furthermore, MCs have been seen in the rat and guinea-pig AV valves, where they exhibited a close relationship with the nerve bundles. Also the chordae tendineae of the guinea-pig showed a moderate population of MCs close to nerve bundles (84). In addition, Ahmed (84) and Ahmed et al. (85) observed that the AV valves and the chordae tendineae of the rat and guinea-pig showed positive immunoreactivity to *i.a.* NPY, SP and CGRP.

It is known that antidromic stimulation of cardiac sensory C-fibers releases CGRP, which increases heart rate, contractility, and coronary flow. C-fiber endings are closely associated with MCs, and CGRP may release MC histamine (86).

MCs and their chemical mediators play a role in cardiac and systemic anaphylaxis. Perivascular and cardiac MCs have been implicated in the pathogenesis of coronary artery spasm, atherosclerosis, and myocardial ischemia (87).

Furthermore, it has been reported that exposure to high-strength electric fields can influence the electrocardiogram (ECG) pattern, the heart rate, and the blood pressure. Jehenson et al. (88) studied the influence of a 2 T static magnetic field on the cardiac rhythm with 24 hours electrocardiographic monitoring in 12 healthy volunteers for 1 hour before exposure, 1 hour during exposure, and 22 hours after exposure. A significant increase in the cardiac cycle length (CCL) was observed after 10 minutes exposure. Jehenson et al. (88) suggested that the CCL increase during exposure could reflect a direct or indirect effect of magnetic fields on the sinus node. In addition, a decrease in heart rate and an increase in sinus arrhythmia have been observed in squirrel monkeys during a 1 hour exposure to a 7 T magnetic field (89).

Electrocardiographic data have demonstrated that a certain correlation exists between acetylcholinesterase activity and the cardiac function (90). Abramov and Merkulova (90) stated that a single 6 hours application of a pulsed EMF resulted in an increased cholinesterase activity in all cardiac structures, besides neurocytes. If the application was continued, cholinesterase activity was progressively decreased and its minimum was observed on the 10th day of stimulation. From the 15th day on, increasing enzymatic activities were observed, various for different enzymes. MCs were noted to appear along the cholinergic nerve fibers. A suggestion was made on a possible exchange between them by the mediator acetylcholine.

From the obtained data of all these studies, it is evident that relevant changes are present in the heart after exposure to EMFs. One could think that the cardiac MCs, with their close relationship to the nervous structures, either are affected and degranulated directly by the EMFs, or indirectly through a neuropeptide pathway.

'Electrosensibility' and 'screen dermatitis'

Johansson et al. (3) studied the effect of EMFs and possible morphological as well as histochemical changes in the skin before and after an open-field provocation, in front of an ordinary TV set, of two patients complaining from skin symptoms due to work at VDTs, i.e. 'screen dermatitis'. They observed certain profound changes in the dermis and epidermis. Using immunohistochemistry, in combination with a wide range of antisera directed towards cellular and neurochemical markers, they could show a high-to-very high number of somatostatin-immunoreactive dendritic cells as well as histamine-positive MCs in skin biopsies from the anterior neck taken

before the start of the provocation. At the end of the provocation the number of MCs was unchanged, but the somatostatin-positive cells had seemingly disappeared.

In another study, Johansson et al. (6; see also Ref. 1) investigated the presence of MCs in skin from patients using histamine-based immunohistochemistry (52,53). From these studies, it was clear that the number of MCs in the upper dermis was increased in the 'screen dermatitis' ($n=15$) patients as compared to normal healthy skin ($n=15$). They could also observe a different pattern of MC distribution in the patient group, namely, the normally empty zone between the dermo-epidermal junction and mid-to-upper dermis had disappeared in the patient group and, instead, this zone had a high density of MC infiltration. Furthermore, in the patient group, the cytoplasmic granules were more densely distributed and more strongly stained than in the control group, and the size of the infiltrating MCs was found to be larger in the patient group as well (1,6). Johansson et al. (3) and Johansson and Liu (1), suggested that the high initial number of MCs could explain the clinical symptoms of itch, pain, edema and erythema in these patients.

Donnellan et al. (7), studied the effects of exposure to electromagnetic radiation on a MC analogue, RBL-2H3. They could observe that the rate of DNA synthesis and cell replication increased, that actin distribution and cell morphology became altered, and the amount of B-hexosaminidase (a marker of granule secretion) released to a calcium ionophore was significantly enhanced, in exposed cultures as compared to unexposed.

Furthermore, Johansson et al. (4) studied possible changes in the facial skin in patients claiming to suffer from 'screen dermatitis', with special emphasis put on neurochemical markers, compared to normal healthy controls. They found clear differences between the two subject groups for the biological markers somatostatin, VIP, CGRP, PHI, NPY, protein S-100, neuron-specific enolase (NSE), protein gene product 9.5 (PGP 9.5) and phenylethanolamine N-methyltransferase (PNMT). All 'screen dermatitis' patients showed a higher number of somatostatin-positive dendritic cells, which is in accordance with previous observations made by Johansson et al. (3) and Johansson and Liu (1).

Johansson et al. (4) suggested that certain markers very well could explain some of the claimed clinical, subjective and/or objective, symptoms. The autonomic markers VIP, PHI and NPY (perhaps also CGRP) may explain the redness and edema. Changes in the CGRP-immunoreactive nerve fibers could be the basis for sensory symptoms, such as itch, pricking pain, and smarting. Furthermore, somatostatin and protein S-100 within epidermal and dermal dendritic cells could account for the general subjective sensation of an on-going inflammation and susceptibility to skin infections as well as the reported sensitivity to ordinary light (cf. Ref. 91).

With regard to these observations one may believe that EMFs influence the neuropeptide content of the skin, which in its turn could affect the MC degranulation and release of *i.a.* histamine. The basis for this could be an EMF-dependent effect directly on the cutaneous, as well as other, nerve fibers. This may be a possible way to explain the clear and profound skin symptoms of 'screen dermatitis' patients.

CONCLUSIONS

Results from the above-mentioned studies show that EMFs affect the MCs and may result in MC degranulation and release of inflammatory substances, including histamine (Fig. 2). It is obvious that the MC, and also the dendritic cell, population is affected by EMFs. However, it is still unknown whether EMFs affect these cells directly or indirectly.

EMFs may primarily affect the MCs, and they will consecutively release mediator substances which, in its turn, activate dendritic cells and their release of somatostatin (Fig. 3). However, EMFs could affect the dendritic cells directly and these cells could then activate MCs' release of inflammatory substances, such as histamine, heparin, serotonin, VIP, etc. (Fig. 3). The third possibility would be that EMFs affect both MCs and dendritic cells directly and degranulate these cells (Fig. 3).

The release of inflammatory mediators from MCs in the human skin results in a local erythema, edema and sensation of itch and/or pain, and maybe the release of somatostatin from the dendritic cells in the skin gives rise to subjective sensations of on-going inflammation and the reported sensitivity to ordinary light. All the above-mentioned cutaneous symptoms are the common symptoms

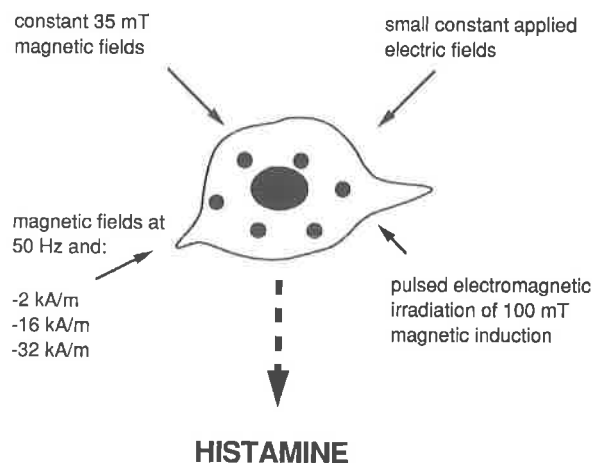


Fig. 2 Summary of known effects of electromagnetic fields (EMFs) on mast cells (MCs). Interactions of EMFs with MCs may result in MC degranulation and release of inflammatory mediators, such as histamine. For further details, see the text.

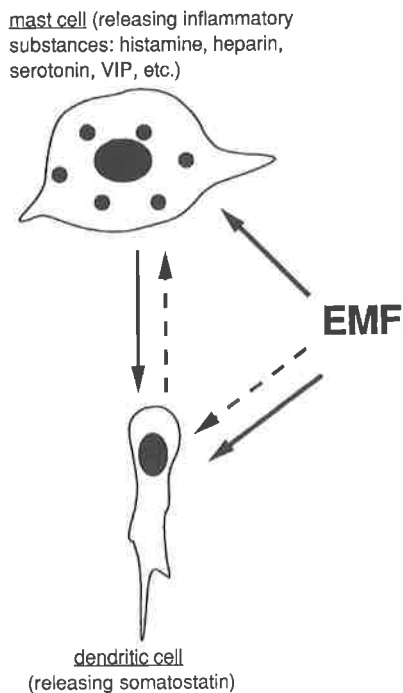


Fig. 3 Schematic illustration of possible effects of electromagnetic fields (EMFs) on mast cells (MCs) and dendritic cells. From observations of several studies (see text) it is clear that certain changes occur in the MC, and also in the dendritic cell, population. The figure illustrates the possible ways in which EMFs could affect these cell populations. For further details, see the text.

that 'screen dermatitis' patients suffer from. In addition, cardiac symptoms have also been reported. MCs are, as described before, also present in human heart tissue. From the results of studies on the interaction of EMFs with the cardiac function, it is clear that relevant changes are present in the heart after exposure to EMFs. These changes may be due to the influence of EMFs on the cardiac MCs and their release of inflammatory mediators. One could argue that the cardiac MCs, with their intimate relationship to the nerves, could be affected and degranulated directly by the EMFs, or indirectly through a neuropeptide pathway.

Thus, it is clear that certain changes occur in different MC populations after electromagnetic/magnetic exposure, and these changes may consequently be a direct cellular response to EMFs. The results of the previously discussed study of Donnellan et al. (7) confirms this assumption.

Finally, if the above reported effects, seen in different laboratory animals, such as mice and rats, as well as in various in vitro situations, would occur in human beings exposed in similar ways, it is not surprising at all to find persons claiming different subjective and objective symptoms, such as itch, flare, edema, etc., after exposure to e.g. mobile telephones, VDTs or fluorescent light. On the

contrary, these persons may very well function as biosensors, thus revealing to the rest of the human population a warning signal that has to be taken seriously!

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Does human β A4 exert a protective function against oxidative stress in Alzheimer's disease?

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Summary The hypothesis is advanced that human β A4 – as opposed to rodent β A4 – may exert a protective function against the iron-induced oxidative stress associated with neurological diseases (notably Alzheimer's disease). Subsequent to its release by the host in response to oxidative injury, human β A4 would interact with Cu^{2+} ions whose level is correlatively elevated, adopting the 'aggregated' structure recently characterized by Atwood et al. (15). Then, depending on the oxidative state – hence the pH – of the medium, it might either return to its original structure if physiological pH is restored, or undergo site-specific copper-mediated oxidation and, finally, degradation. In this context, β A4 pathogenicity could be due to an interfering mechanism preventing the degradation of the oxidized peptide, making its aggregation irreversible and inducing its final deposition. Coordination of side group oxygen donors of the oxidized peptide with 'hard' metal ions occurring in the physiological medium (notably Al^{3+}) might be at the origin of this interference. © 2000 Harcourt Publishers Ltd

INTRODUCTION

The β A4 amyloid peptide is thought to play a key role in the pathogenesis of Alzheimer's disease (AD). Its aggregation is at the origin of the formation of the senile plaques which, along with neurofibrillary tangles (NFTs), are recognized as the pathological hallmark lesions of AD (1–4). The premature appearance of amyloid in the extracellular neuronal space has been evoked as a possible marker for the initial stages of the disease (5). A progressive association between stage of β A4 amyloid plaque formation and prevalence of neuronal cell injury has been recently demonstrated in AD brains (6), and β A4 amyloid deposition has been shown to precede NFT formation by about two decades (7) (no relation of cause and effect between β A4 amyloid deposition or exposure and NFT formation has yet been firmly established, however (4, 8)).

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Soluble β A4 peptide is produced constitutively by normal cells (9). It consists of a sequence of up to 40–43 residues that results from the proteolytic cleavage of a ubiquitously expressed transmembrane glycoprotein: the β A4 amyloid protein precursor (APP). The 28 NH_2 -terminal amino acids of the β A4 sequence are part of the extracellular domain of APP, the remaining 14–15 being part of the APP transmembrane domain (10). Neurotrophic in its original soluble state, the β A4 peptide becomes neurotoxic following aggregation and precipitation (11,12). Aggregation of the human β A4 sequence has been obtained in vitro through interaction with several metal ions (13–15), as well as via metal-catalysed oxidation, the latter process mainly affecting histidine and tyrosine residues (10,16). (By contrast, the rodent β A4 sequence – which only differs from the human peptide by three amino acid substitutions: Arg→Gly, Tyr→Phe and His→Arg at positions 5, 10 and 13, respectively – displays a different aggregational behaviour, which is in line with the fact that rodents rarely develop AD (16).) On the other hand, the reversible aggregation properties of β A4 have been suggested to play a role in maintaining regional structural integrity (15) at local injury sites where β A4 deposits are known to rapidly appear following injury (17,18). The recent finding that β A4 levels in