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Electrochemical Involvement in Illnesses

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Abstract

Extensive literature exists in relation to electrochemical involvement in human illnesses. Examples included in the present review are cancer, bone fracture, injury from cell phones and electrical transmission lines, Parkinson's disease, Alzheimer's, depression, stroke and others. An important aspect is involvement with cell signaling and radical formation. The relationship to reactive oxygen species and oxidative stress, resulting in toxicity, is discussed. Various reports address the beneficial effects of antioxidants in countering the harmful influences. Evidence shows the important participation of electrochemistry in illnesses, in addition to other factors in a multifaceted manner.

Key words: *Electrochemical; Brain; Bone; Cancer; Alzheimer 's; Parkinson's; Oxidative stress; Reactive oxygen species*

Abbreviation: ET: Electron transfer; ROS: Reactive oxygen species; AO: Antioxidants; OS: Oxidative stress; EMF: Electromagnetic field

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Introduction

Recent reviews document the importance of electrochemistry, receptors and cell signaling in many aspects of biology and medicine [1-9]. Approach to electrochemical involvement in illness. Although there is extensive literature on electrochemistry and individual illnesses, scant attention has been given to unifying, mechanistic application entailing a broad spectrum of afflictions. This review addresses the electrochemical approach with focus on a wide variety of areas including cancer, bone injury, Parkinson's, Alzheimer's, depression, stroke, migraine and radiation from mobile phones, radio and power lines. The role could be in illness generation or as therapy. Electromagnetic fields (EMFs) have been used as therapeutic agents during almost a half-century [10].

The widespread involvement of electrochemistry is illustrated by the following examples [2]. Initiation and evolution of life involved chemical compounds and energy sources, such as the sun and electromagnetism. Bioelectrical phenomena play a vital role in life processes. Among the intrinsic features of living systems are the separation, transport and storage of electrical charge [11]. The participation of electron transfer (ET) is recognized as one of the essential requirements for electrochemical communication between molecules. An EMF is associated with the mobile, charged electron. Electromagnetic forces are primarily responsible for structure of matter from atoms

to more complex substances [12] and have played a dominant role in cell division and other processes in primitive cells as well as modern eukaryotic ones. The preponderance of bioactive substances or their metabolites incorporate ET functionalities, which, we believe, play an important role in physiological responses. The main group includes quinones (or phenolic precursors), metal complexes (or complexors), aromatic nitro compounds (or reduced nitroso or hydroxylamine derivatives) and conjugated iminiums (or imines). There are two principal pathways that can result from ET, one being redox cycling with generation reactive oxygen species (ROS) and oxidative stress (OS). The other involves interaction with the central nervous system (CNS).

ET is probably the most prevalent and important process in chemical transformation. The generality and unifying aspect are demonstrated by involvement in all areas of the physical and biological sciences. Among the numerous subjects addressed are enzymes, membranes, chromosomes, histamine, receptors, the Hofineister effect, plant chemistry, evolutionary development, neurotransmission, DNA, phosphorylation, sulfation, metal ions and anesthetics [2].

However, it should be recognized that biological action is often multifaceted, a concept which can also be applied to the electrochemical-illness combination. Among the various factors, which play a role in illnesses, one of the most important is ROS. Earlier reports provide evidence for participation by ROS involving anti-infective [13] or anticancer [14] agents. The action has been designated as phagomimetic since it emulates the immune system [15]. The ROS approach can be applied both to therapeutic action and to toxicity. In the case of cancer, the mechanistic framework rationalizes the Haddow paradox in which a substance can act as both a carcinogen and anticancer agent [16].

Although the present review covers many illnesses, there are others, which are not included. In some cases, original references can be found in the reviews or articles.

Cancer

There is considerable literature on involvement of electrochemical effects in cancer [2]. Individuals occupationally exposed to EMFs undergo an increased risk of brain tumors, particularly astrocytomas [17]. For example, a study revealed more risk of brain tumors in electric utility workers linked in a dose-dependent manner to exposure to EMF. Employment in occupations that entail exposure to EMF presents an elevated risk of 1.7 for all gliomas, and a risk of 10.3 for astrocytomas. [2] Though a recent study did not support the hypothesis of an increased risk of brain cancer associated with occupational exposure to magnetic fields, a metaanalysis of 52 studies recently concluded that there is a small, pervasive association between brain cancer and exposure to EMF. The biological basis for such association, i.e., the cellular and molecular mechanisms underlying these effects of EMF are, however, poorly understood.

A prevailing hypothesis is that EMFs may not cause cancer initiation, but may instead act as a promoter [17]. Several studies suggest possible mechanisms to explain the association between EMF exposure and cancer [2]. One of the most interesting and unifying hypotheses involves interaction of EMFs with signal transduction systems. Specifically, EMFs may influence the signal transduction cascade at the level of the cell membrane, trigger changes in calcium influx and/or receptor binding, and induce gene expression and protein synthesis, which may ultimately lead to cell proliferation. Preliminary evidence also suggests that exposure to EMFs cause an increase in protein kinase C activity. PKC is recognized as a key component of the cellular signal transduction cascade and has been implicated in modulating the expression of certain genes and regulating cell proliferation. EMFs that are not mutagenic per se are often able to increase mutation and tumor frequencies [18].

Bone injury repair

Appreciable attention has been paid to the practical, medical effects of electrical field exposure on bone injury [2]. There has been renewed interest in the use of magnets for enhancing tooth movements [19]. The major premise upon which magnetic effects alter cell reactions is based upon electrically based theories of cellular signaling or perturbation of polar proteins within the cell membrane. The two major theories are based upon electrically based phenomena, i.e. piezoelectrici ty and streaming potential [2].

Both mechanical and electrical signals have been shown to regulate the synthesis of extracellular matrix and may do so through the stimulation of signaling pathways at the cell membrane resulting in the appearance of intracellular second messengers, particularly cyclic nucleotides [20]. The therapeutic use of electric fields is derived from the observation that when bones are placed under mechanical load (stress) the deformation (strain) is accompanied by an electrical signal which is related to strain characteristics. This strain-related or strain-generated electric potential has been hypothesized to consist of information transfer to the osteocyte regarding the nature of its mechanical environment and the state of the extracellular matrix. The origin of the electric signal was thought initially to be related to deformation of the crystalline structure of extracellular matrix collagen·, involving the piezoelectric effect. Other data, however, have suggested that alterations in fluid flow might produce electrokinetic events, specifically streaming potentials, which might be partly or wholly responsible for the observed electric potential.

There are different transduction pathways for ultrasound and pulsed electromagnetic field stimulation that lead to an upgrade of osteoblast proliferation, with their pathways all leading to an increase in cytosolic Ca^{2+} and activation of calmodulin [21]. These findings offer a biochemical mechanism to support the process of ultrasound and pulsed electromagnetic field- induced enhanced healing of bone fractures. Pulsed EMFs affect phenotype and connexin 43 protein expression [22]. The mechanism by which EMFs affect bone turnover are unclear. They can directly affect osteoclastic cells, and there is evidence that cells in the osteoblast lineage are sensitive to EMFs. Pulsed EMFs can influence osteoblst-like cells by increasing transforming growth factor beta-1 (TGF-P 1) levels, but decreasing levels of prostaglandin E2 (PGE2) in the conditioned media. Pulsed EMFs also increase TGF-P 1 production by atrophic and hypertrophic nonunion cells. Others have shown that EMFs increase ostoblastic proliferation, and extracellular matrix production.

There are recent articles dealing with electric and EMFs that regulate extracellular matrix synthesis and stimulate repair of fractures and nonunions [23]. The study suggests that exposure to EMFs can accomplish the following: (a) regulate proteoglycan and collagen synthesis and increase bone formation in models of endochondral ossification, (b) accelerate bone formation and repair, (c) increase union rates in fractures, and (d) produce results equivalent to bone grafts.

Pulsed EMFs with different intensities could regulate osteoclastogenesis, bone resorption, osteoprotegrin, NFkappaB-ligand, and macrophage-colony-stimulating factor in marrow culture system [24]. A clinical study with 64 patients undergoing hindfoot arthrodesis showed that the adjunctive use of pulsed EMF increases the rate and speed of radiographic union of joints [25]. A similar study with 100 patients with symptomatic pseudarthrosis lumber spine fusion, pulsed EMF was shown to be an effective nonoperative salvage approach to achieving fusion [26]. A 2003 review entails the therapeutic uses of electromagnetic treatment in various other bone disorders, such as musculoskeletal, congenital pseudoarthrosis, osteoporosis, hip arthroplasty, rheumatoid arthritis, osteoarthritis, spinal fusion, rotator-cuff tendinitis, lateral humeral epicondylitis, and interbody lumbar fusion [10].

Mobile phones, radio and electric power lines

This area has attracted appreciable attention in recent years [2]. In a study, detailed molecular mechanism by which electromagnetic irradiation from mobile phones induces the activation of the extracellular-signal regulated kinase cascade and how it induces transcription and other cellular processes were described [27]. Upon irradiation (mobile phone frequencies), cascades are rapidly activated in response to various frequencies and intensities of EMF. The first step is mediated in the plasma membrane by an oxidase, which rapidly generates ROS. These ROS then directly stimulate matrix metalloproteinases and allow them to cleave and release heparin-binding epidermal growth factor, which, in turn, further activates the extracellular-signal regulated kinase cascade. Mobile phone radiation-induced activation of hsp27 may (i) facilitate the development of brain cancer by inhibiting the cytochrome c/caspase-3 apoptotic pathway and (ii) cause an increase in blood brain barrier permeability through stabilization of endothelial cell stress fibers [28]. Authors postulate that these events, when occurring repeatedly over a long period of time, might become a health hazard because of the possible accumulation of brain tissue damage. Furthermore, other brain damaging factors may co-participate in mobile phone radiation-induced effects.

A study demonstrated the effects of 900 MHz EMF emitted from cellular phone on brain tissues and also blood malondialdehyde, glutathione, retinal, vitamin D3, tocopherol and catalase enzyme activity of guinea pigs [29]. Results indicated production of OS in brain tissue. A similar study showed 900 MHz mobile phone-induced oxidative endometrial impairment [30]. The modulation of OS with vitamin E and C reduces the endometrial damage, both at biochemical and histological levels. Similar exposure also enhanced lipid peroxidation and H_20_2 content accompanied by diminished antioxidative enzyme activity, indicating OS could be partly due to reduced activities of AO enzymes in duckweed [31]. Rats exposed to EMF showed increase in malondialdehyde levels and decrease in GSH levels [32]. A study demonstrated protective effects of melatonin and caffeic acid phenethyl ester (CAPE) against retinal oxidative stress in long-term use of mobile phone [33]. Mobile phone-induced myocardial OS protection by the AO CAPE was shown [34]. CAPE may prevent the 900 MHz EMF-induced oxidative changes in liver by ROS, reducing and increasing AO enzyme activities [35]. Radio-frequency electromagnetic radiation from mobile phones induces OS and reduces sperm motility in rats [36]. Thus, semen quality and male fertility may be negatively affected. The protective effects of the AOs N-acetyl-L-cysteine and epigallocatecin-3-gallate on electric field-induced hepatic OS was reported [37]. Results indicate significant increase in the levels of oxidative products e.g., malondialdehyde, and significant decrease in the AO enzyme SOD; GSH-Px activity was affected on exposure to EMF. Addition of AOs resulted in the reduction of OS prior to EMF application.

Results demonstrate 60-Hz sinusoidal MF-activated cell growth inhibition of prostate cancer *in vitro* [38]. Apoptosis together with cell cycle arrest were the dominant causes of the MF elicited cell growth inhibition, mediated by MF-induced ROS. These results suggest possibility of using 60-Hz MF in radiation therapy of prostate cancer. There is formation of ROS in cells after exposure to 900 MHz radio frequency radiation [39]. Results showed that hydrogen peroxide is produced in aqueous solutions under exposure to electromagnetic radiation as a result of the influence of heat and thermoacoustic waves [40]. The induction of intracellular ROS by blue light implies that redox effects may mediate the cellular responses. This result suggests the opportunity to mitigate any effects of direct or coincident exposure during dental treatment via AO [41]. A recent study suggests that 872 MHz RF radiation might enhance chemically induced ROS production and thus cause secondary DNA damage [42].

A study suggests that mobile telephone radiation leads to oxidative stress in corneal and lens tissues and that AOs, such as vitamin C, can help to prevent these effects [43]. Mobile phones caused oxidative damage biochemically by increasing the levels of malondialdehyde, carbonyl groups, xanthine oxidase activity and decreasing catalase activity, and that treatment with melatonin significantly prevented oxidative damage in the brain [44]. Increase in malondialdehyde levels of renal tissue and also the decrease in renal SOD, catalase, GSH peroxidase activities demonstrate the role of OS induced by mobile phone exposure. Melatonin, via its free radical scavenging and AO properties, ameliorated oxidative tissue injury in rat kidney [45]. A similar study suggested that EMF at the frequency generated by a cell phone causes OS and peroxidation in the ertythrocytes and kidney tissues from rats. In the erythrocytes, vitamin C seems to protect against the OS [46]. A citrus flavoglycoside, naringin protects mouse liver and intestine against the radiation-induced damage by elevating the AO status and reducing the lipid peroxidation [47]. EMF is a stressor agent that induces an imbalance between ROS generation and AO defense response [48].

Cell signaling

There is extensive literature on the effects of EMFs on cells. Interaction with signaling systems is a potential mechanism by which very low-energy EMFs might produce metabolic responses in the body [49]. As an example, one metabolic process in which the physiological effects of low-energy EMFs is well established is the healing of bone fractures (see section on Bone Injury Repair). The process of regulation of bone turnover and healing is reviewed in the context of clinical applications of electromagnetic energy to the healing process. A hypothetical molecular mechanism is presented that might account for the observed effects of EMFs on bone cell metabolism in terms of the field interference with signal transduction events involved in the hormonal regulation of osteoblast function and differentiation. Exposure to 900 MHz EMF induces an unbalance between pro-apoptotic and pro-survival signals in leukemia cells [50]. The relationship of electrochemistry to cell signaling is treated in more detail in recent reviews [1,2].

Parkinson's disease

Various studies are reported on electrical therapy for Parkinson's disease [2]. Rapid electrical stimulation is safe and efficient in treatment of patients [51,52]. The literature contains similar findings [53,54]. In MPTP-treated cats, recordings suggested that dopamine is the predominant electroactive species [55]. Determination of redox ratios gave a similar result. In the dorsal striatum of recovered cats, seratonin, rather than dopamine, appears to be the predominant electroactiye species. Electrical deep-brain stimulation (DBS) is a valuable complement to pharmac9logical treatment [56]. DBS improves Parkinson's motor symptoms by inducing global changes in- firing pattern and rate [57]. Experimental electrical stimulation of the dorsal columns in the spinal cord restores locomotion. High frequency stimulation (HFS) of the subthalmic nucleus dramatically alleviates motor symptoms in Parkinson's disease [58]. Changes in the temporal firing patterns of neurons underlie the beneficial effects of HFS in Parkinson's disease [59]. A study indicates that the mechanism of HFS is complex [60]. HFS induces akinasia and low frequency stimulation induces tremor [61]. Transcranial magnetic stimulation produces transient improvement in dysfunction [62].

A study showed that static magnetic field exposure reproduces cellular effects of a Parkinson's disease drug candidate [63]. SMF reproduced several responses, including altered calcium flux, increased adenosine triphosphate (ATP) levels, reduced cyclic adenosine monosphosphate (cAMP) levels, reduced nitric oxide production, reduced phosphorylation, and.inhibition of proliferation and iron uptake.

A report demonstrated the beneficial effect of the left prefrontal repetitive transcranial magnetic stimulation on depression in Parkinson's disease, the effect lasting for 30 days after treatment [64]. Long-term therapy with levodopa and dopamine agonists in Parkinson 's disease patients is complicated by the development of fluctuations in motor response, such as levo-dopa induced dyskinesia. Data showed repetitive transcranial magnetic stimulation improves the motor response [65]. Repetitive transcranial magnetic stimulation decreased the levels of cycloxygenase-2 and tumor necrosis factor-alpha in rat substantia nigra, and prevented the fall of dopamine in striatum of rats with Parkinson's disease [66].

High frequency repetitive magnetic stimulation over supplementary motor area improves bradykinesia in Parkinson's disease patients [67]. A similar study showed the beneficial effects of transcranial magnetic stimulation on Parkinson motor functions [68]. A 2008 review entails the beneficial effects ofrepetitive transcranial magnetic stimulation in Parkinson 's disease [69].

Alzheimer's disease

Alzheimer's disease is a neurodegenerative disorder clinically characterized by a progressive cognitive decline that affects memory and other functions, as well as mood and behavior. It is the most common type of dementia, which affects more than 35 million people all over the world. The disease is characterized by extracellular formation of AP amyloid plaques and intracellular deposition of neurofibrillary tangles in specific cortical areas; this process leads to loss of neurons and white matter, amyloid angiopathy, inflammation, and oxidative damage [70].

Transcranial magnetic stimulation is a safe, noninvasive and painless technique widely employed to explore brain functions. From about 15 years ago, it provides a valuable tool for studying the pathophysiology of Alzheimer's disease. A recent review details the application of this technique to this disease [71].

A report showed that electromagnetic field treatment protects against and reverses cognitive impairment in Alzheimer's disease in mice, suggesting that EMF exposure may represent a non-invasive, non-pharmacologic therapeutic approach against Alzheimer's disease and an effective memory-enhancing approach in general [72].

Data provide initial evidence for the persistent beneficial effects of repetitive transcranial magnetic stimulation on sentence comprehension in Alzheimer's patients [73]. A similar study showed that electromagnetic stimulation improved the concept study and naming in Alzheimer patients [74,75].

Vascular dementia is a clinical syndrome that encompasses a wide spectrum of cognitive disorders caused by cerebrovascular disease. The subcortical ischemic form of vascular dementia is clinically homogeneous and a major cause of cognitive impairment in the elderly. Vascular lesions contribute to cognitive decline in neurodegenerative dementias and Alzheimer's disease. A review entails the use of transcranial magnetic stimulation in vascular dementia [76].

Repetitive transcranial magnetic stimulation induced biochemical changes in specific enzymatic activities, trace metal concentrations, such as zinc and copper in saliva, plasma and erytluocytes and induction of novel salivary proteins, with sensory improvement in patients with taste and smell dysfunction [77]. These type of stimulation improved taste and smell in patients with neurological disorders, such as Alzheimer's and Parkinson's.

Depression

Favorable results occur in electrotherapy of patients with depression [2]. Electrical treatment obtained good outcomes with high safety and tolerability [78]. There is evidence for electrical nerve stimulation as the treatment of choice for pain and depression [79]. Another investigation deals with the influence of transcranial current stimulation coupled with repetitive electrical stimulation on depression [80]. Electrochemical evidence supports a direct relationship between 5-HT and cytoskeleton in the control of mood [81]. Two recent reviews address the use of repetitive transcranial magnetic stimulation in the treatment of depressive disorders [82,83]

Depression is often a serious and debilitating illness in adolescents. Unfortunately, a significant number of adolescents do not respond to antidepressant medications or psychotherapy. Repetitive transcranial magnetic stimulation is a treatment shown to benefit depression in adults [84]. A similar study showed that this type of stimulation serves as an augmenting treatment method in drug-resistant depression [85].

A report showed that daily left prefrontal repetitive transcranial magnetic stimulation for acute treatment of medication-resistant depression improved the symptoms [86]. A study highlights the importance of spontaneous neural activity during repetitive transcranial magnetic stimulation and demonstrates that the stimulation technique can induce long-lasting effects on brain derived neurotropic factor and GluRl which may underlie the clinical benefits of this treatment in neuroplasticity -related disorders [87].

A report suggests that novel methods of repetitive transcranial stimulation, such as priming stimulation, theta-burst stimulation and deep transcranial magnetic stimulation, appear to be promising in treatment [88]. Preliminary data indicate that the stimulation method is effective in the treatment of depression in patients with schizophrenia [89]. The technique applied over the left dorsolateral prefrontal cortex might induce positive effects in patients with mild cognitive impairment of the vascular type without dementia [90]. A study provides evidence that therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression showed improvement of greater than 50% in their depression ratings [91].

Cerebral ischemia (stroke)

Aphasia is a common symptom after left hemisphere stroke. Neuroimaging techniques over the last 10-15 years show two general trends: patients with small left hemisphere strokes tend to recruit perilesional areas, while patients with large left hemisphere lesions recruit mainly homotopic regions in the right hemisphere. Non-invasive transcranial magnetic stimulation and transcranial direct current stimulation have been employed to facilitate recovery from post-stroke aphasia [92].

A report showed that repetitive transcranial magnetic stimulation improved the language outcome in-patient with chronic crossed aphasia [93]. The approach results in improved language benefits that generalize beyond naming to include other aspects of language production [94]. Related studies also showed the beneficial effects in human memory therapy, motor learning, aphasia and memory formation [95-97].

A review deals with the transcranial magnetic stimulation in poststroke aphasia and neurorehabilitation [98]. Several other researchers report the beneficial effect of this technique in post stroke patients [94, 99-103]. A 2003 review entails therapeutic use of pulsed magnetic-field exposure and covers literature prior to this period [10].

Migraine headache

A report showed that single-pulse transcranial magnetic stimulation may offer a nonpharmacologic, nonbehavioral therapeutic approach to the currently prescribed drugs for patients who suffer from migraine [104].

Others

The interaction of static magnetic fields (SMFs) with living organisms is a rapidly growing field of investigation [105]. However, despite an increasing number of studies on the effects of the interaction of SMFs with living organisms, many gaps in our knowledge still remain. One reason why it is extremely important to understand the mode of action of magnetic fields on living organism is the need to protect human health in consideration of the increasing introduction of new technologies, such as magnetically levitated trains and the therapeutical use of magnetic fields (e.g., magnetic resonance imaging (MRI, coupling of magnetic field exposure with chemotherapy.

The lack of knowledge of the morphological modifications brought about by exposure to moderate-intensity SMFs prompted the authors to investigate the bioeffects of 6 mT SMFs on different cell types, by means of light and electron microscopy, confocal laser scanning microscopy and immuno- or cytochemistry [105]. The morphological modifications related to cell shape, cell surface, cytoskeleton, and plasma membrane expression of molecules and carbohydrate residues were studied. The effects of exposure to moderate-intensity SMF on apoptosis, apoptotic related gene products, macrophagic differentiation and on phagocytosis of apoptotic cells in primary cell cultures were studied. Results showed moderate-intensity (6 mT) SMFs induced modifications of cell shape, cell surface and cytoskeleton. Apoptosis was influenced in a cell type-dependent manner.

Several physical mechanisms have been proposed to account for the initial interactions with cells [106]. Magnetic fields interact with moving charges in cells and change their velocities, as in the classic interaction of magnetic field with any moving charge. Charge flow associated with a biological function, as for enzyme activity, has been demonstrated in Na, K- ATPase and cytochrome oxidase reactions. Interaction of weak EMF with living cells is a most important, but unresolved biophysical problem [107]. Regulation of ion and substrate pathways through microvilli provides a possible theoretical basis for the comprehension of physiological effects of even extremely low magnetic fields.

Erythroleukemia K562 cells and lentil root protoplasts have been subjected to pore-forming electric fields suitable for transfection experiments [108]. Evidence showed the amount of hydroperoxides formed in cell membranes of both cell-types is a function of field strength applied. On the other hand, electroporation-induced lipid peroxidation paralleled the enhancement of membrane permeability and was associated with greater membrane fluidity. The membrane hydroperoxides formed upon electric shock enhanced cell luminescence, and lipoxygenase activity appeared to be involved in the process.

Electrical signaling is involved with changes in membrane potential and electrical impulses in nerve cells for use in communication with other cells [109]. The process entails conversion of electrical signals into chemical ones. There is knowledge of phosphorylations that affects enzyme activity solely by electrostatic effects.

Data showed electrical stimulation accelerates axon outgrowth and target muscle reinnervation in animals and humans [110]. Pulsed electromagnetic fields reduced diabetic neuropathic pain and stimulated neuronal repair [111]. A related study showed electrical stimulation promotes motoneuron regeneration [112]. Various other disorders have been discussed in relation to therapy [1].

Conclusion

Electrochemistry has been shown to play an important, beneficial role in a variety of human illnesses. Evidence indicates interaction with the *in vivo* electrical system in both a positive and negative manner. It is important to recognize involvement of a multifaceted operation, including ET-ROS-OS-AO.

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