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Research Idea

Electromagnetic radiation as antiviral treatment with a focus on Rabies post-exposure prophylaxis

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Abstract

Shortwave and microwave diathermy devices are commonly used in physical therapy as heating treatment. The rise in temperature occurs due to the flow of electric current in the treated area. Ions are evenly distributed in a predicted pattern from skin to deeper tissues. We hypothesise that the diathermy physiotherapy devices (DPDs) can be repurposed as a means of neutralisation of the Rabies virus (RABV) by exploiting the generated electric charges. In order to minimise the ohmic heating of the tissue, the pulsed output of the diathermy devices is preferred where the 'on' time of active energy emission is considerably shorter than the 'off' time. RABV proteins mediating cell invasion, cytoplasmic replication and budding, contain polar components that can be adversely affected by non-thermal electric phenomena. Repurposed DPDs can replace the Rabies immunoglobulin (RIG) by targeting the site of inoculation i.e. the area of the animal bite, provided that the delivered electric charges can reduce pathogenicity by altering key viral proteins. The modality is advantageous compared to conventional RIG since it can theoretically neutralise all *Lyssavirus* species, is not limited by the compartment syndrome, can intercept RABV even after it gains access to the peripheral neural network where conventional post-exposure prophylaxis is ineffective and is cost-effective in the long term. The principle of physical alteration of vulnerable proteins by electricity delivered by electromagnetic radiation is not limited to RABV, but may be applied to a spectrum of viral pathogens.

Keywords

post-exposure prophylaxis, Rabies, diathermy, magnetic field therapy, electric stimulation therapy, immunoglobulins, antiviral agents

Background

Rabies is a dreadful disease with dramatic clinical course and almost 100% mortality. The causative agent is the Rabies virus (RABV), a bullet-shaped, enveloped, negative-sense RNA virus, 180 nm long and 60 nm wide. A genome of approximately 12,000 bp encodes five proteins: nucleoprotein N, polymerase L, phosphoprotein P, matrix protein M and glycoprotein G (Rupprecht 1996). The envelope is a lipid layer acquired from the host cells during the process of budding. Glycoprotein G appears as spikes protruding from the envelope and has well-known antigenic properties, whereas protein M supports the structure of the viral particle (Rupprecht 1996,Schnell et al. 2010,Buthelezi et al. 2016).

RABV is inoculated by a bite or scratch inflicted by an infectious animal. The virions move passively at the intercellular space with a pace of 12-24 mm/day and enter nerve cell axons through neuromuscular junctions or sensory terminals. While inside the neural network, the virions are inaccessible to antibodies. Subsequently, RABV is transported from peripheral nerves to the brain following a centripetal route. Once RABV reaches the brain, a progressive encephalitis occurs with an almost invariably fatal outcome (Mahadevan et al. 2016).

In the majority of cases involving bite or scratch by an animal, only a theoretical risk assessment for RABV infection is possible. Animals appearing asymptomatic during the incident do not exclude transmission (Burgos-Cáceres 2011). The process of animal evaluation is complex and requires a series of actions in due time, i.e. identifying the animal, monitoring by a veterinarian for a 10-day period and communications amongst stakeholders (Abdella et al. 2022). The laboratory screening can provide a direct diagnosis, but requires the sacrifice of the animal.

Often, even a remote theoretical risk of exposure to Rabies warrants the administration of post-exposure-prophylaxis (PEP) i.e. Rabies vaccine and, depending on type of exposure, Rabies immunoglobulin (RIG). According to WHO guidelines, RIG must be administered if the epidermis is penetrated (category III of exposure) (World Health Organization 2018). The vaccine induces a gradual development of active immunity, whereas the local infiltration of the tissue with RIG directly inactivates virions.

Even though PEP is a crucial intervention for the prevention of infection, the Rabies vaccine and especially the RIG are often in short supply. The topical infiltration of RIG at the site of trauma where it is highly effective (World Health Organization 2018) may not be feasible due to anatomical constraints or the compartment syndrome, for example, fingers, toes, ears (Hwang et al. 2020). Anaphylaxis due to RIG is not frequent, but may occur (World Health Organization 2018). The high cost of RIG is a serious consideration that limits the availability (Blaise and Gautret 2015). The currently available vaccine and RIG confer only partial protection against European Bat Lyssaviruses (EBLV-1, EBLV-2) (Echevarría et al. 2019) and are not considered effective against other *Lyssavirus* species, such as the Mokola virus (MOKV), Lagos bat virus (LBV) and West Caucasian bat virus (WCBV) (Weyer et al. 2008). The administration of RIG is meaningful for a short period after the incident as long as the virions have not yet entered the neuronal cells. The majority of the victims seek medical help without delay; however, late admissions also occur (Dougas et al. 2019). The likelihood of the virus having entered the neuronal network where it remains shielded from RIG or vaccine-induced antibodies increases with the elapsed time from the exposure.

Diathermy physiotherapy devices

The hyperthermia achieved by the diathermy physiotherapy devices (DPDs) in common physical therapy practice is due to the phenomenon of heat generation when electric current flows through a conductor (living tissues) according to Joule's and Ohm’s laws (Power = V^2/R), where V is voltage and R is resistance (Joule effect) (Song et al. 2021). The electric current has a wave-like form with rapidly oscillating polarity and magnitude at very high radio frequencies (RF). RF is a non-ionising emission of electromagnetic waves up to 3,000 GHz (Shellock 2000). Shortwave (13 - 41 MHz) and microwave (> 300 MHz) RF diathermy devices are commonly used for physical therapy of superficial layers and deep-seated muscles by hyperthermia, hyperaemia and analgesia (Garrett et al. 2000,Fu et al. 2019).

Inductive DPDs use a drum applicator (monode) where a rapidly oscillating (RF) electric current passes through a coil and a magnetic field is generated according to Maxwell’s laws of electromagnetism. The magnetic flux is driven by the monode to the target area and a reactive circular electric current is induced within the tissue, perpendicular to the magnetic lines (Eddy current) (Fig. 1). The hyperthermia is caused according to the general law of resistive “Ohmic” production of heat; however, the presented hypothesis relies on the electrical phenomena and not in the thermal ones.

The magnetic field and the accompanying Eddy current reach deep tissues, without being hindered by skin, bones, tendons or other high-density structures. The local electric current is affected by factors such as wattage, frequency, tissue water content and distance from source (Giombini et al. 2007). A depth of 3-5 cm of effective penetration under the skin is reported, whereas others report an effective depth of up to 8 cm (Merrick 2012 ,Draper et al. 2013).

The capacitive DPDs generate an oscillating electrostatic field in the RF range (shortwave or microwave frequencies) (Sousa et al. 2017) between the condenser electrodes (Fig. 2). Ohmic heat occurs due to the passage of electric current through a conductor (tissue). Compared to the inductive DPDs, the capacitive ones drive the electric current predominantly to the superficial layers.

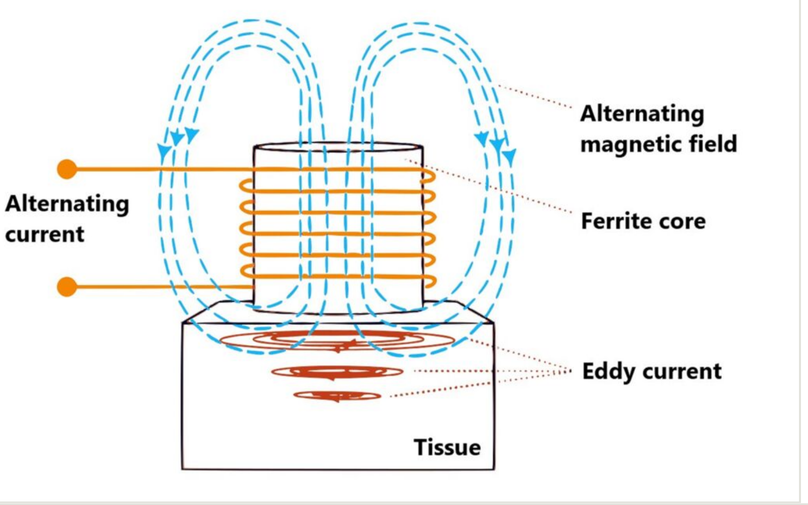

Figure 1. doi

The principle of operation of the inductive physical diathermy devices. The alternating magnetic field generated by AC current induces a flow of electrons (Eddy current) perpendicular to the magnetic field. According to the hypothesis, the electrical phenomena can be exploited to adversely affect viruses in the targeted tissue. The topical hyperthermia occurs as the current passes through the ohmic resistance of the tissue and is not central to the hypothesis.

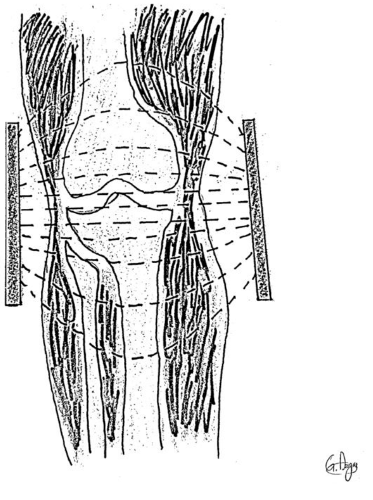

Figure 2. doi

Drawing of a capacitive diathermy physiotherapy device applied at the knee area. The high frequency electric field (dotted lines) formed between the two parallel condenser electrodes penetrates skin, soft tissues and bones.

Inductive and capacitive DPDs distribute the electric current to the superficial and deeper tissues in a predictable pattern.

Both types of DPDs have two modes of application, the continuous mode and the pulse mode. The continuous mode is simply a non-stop RF emission towards the target, highly efficient for generating deep tissue heat. In the pulsed mode, RF is actively emitted during 'on' time (pulse) which is a fraction of the duration of the 'off' time and, therefore, the total energy delivered to the patient is relatively low, even though the peak power during the 'on' time can be quite high. The pulse has a typical duration of 20-400 microseconds and the pulses may range from 20-800 per second. Due to the less amount of delivered energy for the same time of application, the pulsed diathermy generates little or no heat and is preferred when the desired result is electric excitation rather than deep tissue heating (Masiero et al. 2020).

Pulsed shortwave inductive DPDs offer an efficient delivery of the electric energy to the tissues with a minimal risk of thermal damage and the least safety concerns (Laufer and Dar 2012,Draper et al. 2013,Masiero et al. 2020).

Hypothesis

The central hypothesis is the application of electricity for the neutralisation of RABV and other Lyssaviruses as a replacement of RIG in post-exposure prophylaxis. The delivery of electric energy to the target tissue is achieved by repurposed shortwave or microwave diathermy physiotherapy devices (DPDs), commonly used in physical therapy. These devices accomplish hyperthermia by driving electric current through the ohmic resistance of the tissues (Ohm's law). The flow of ions is predictably distributed in a defined surface and depth of the targeted area unhindered by soft or hard anatomic structures. The rise of tissue temperature is a side effect of the electric phenomena and is not important in the present hypothesis. However, heat may exacerbate the bleeding of an open wound inflicted by animal and can even increase infectivity by enhancing local migration of virions. Therefore, the pulsed mode of DPD application is preferred over the continuous mode due to the negligible thermal effect (Masiero et al. 2020).

RABV is surrounded by a host-derived lipid bilayer (envelope) acquired from the invaded cell during exocytosis. In general, enveloped viruses are considered more vulnerable to environmental stressors compared to non-enveloped viruses that are enclosed in a sturdy capsid (Hirneisen et al. 2010, Vasickova et al. 2010, Khadre and Yousef 2002). Proteins that play a major role in RABV pathogenesis contain polar domains. According to the hypothesis, polarity is a property indicating potential susceptibility to electric current. The ionic flow might alter the stereochemical structure and the functional properties of the viral proteins and adversely affect pathogenicity. DPDs can drive electromagnetic energy and electric current to the inoculated virus particles at the site of exposure (e.g. bite area). The physical history, the protein polar profile and the demand to directly intercept virions at the site of inoculation as an alternative to RIG, render RABV eligible for the study of the in vitro/in vivo effects of DPDs. Nevertheless, the ionic effect caused by DPDs may also apply to a variety of viruses that contain susceptible proteins.

The inductive DPDs generate a rapidly oscillating magnetic field that easily penetrates tissues. According to established Laws of Physics, a circular electric current is spontaneously formed, perpendicular to the magnetic lines occurring as a reaction at any change of the magnetic flux ("Eddy current"). Inductive shortwave pulsed output DPDs efficiently distribute the electric current within the treated tissue, exhibit a good safety profile and are proposed as the core diathermy devices. Fig. 3 illustrates an example of a repurposed inductive DPD for neutralising RABV that was inoculated by an animal bite at the gastrocnemius area.

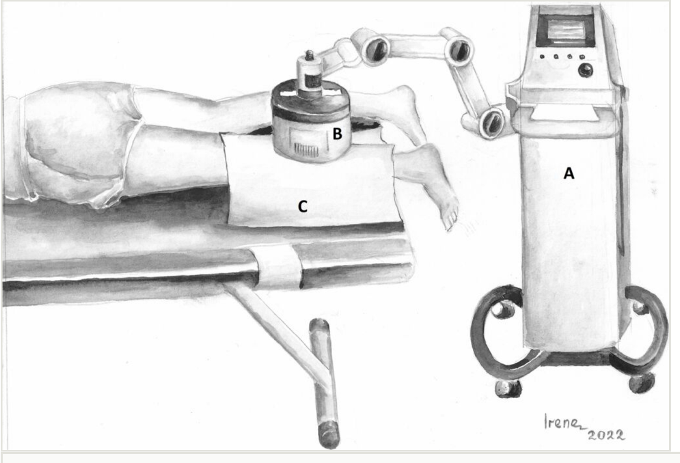

Figure 3. doi

Example of the proposed use of an induction diathermy physiotherapy device (A) to a victim bitten by a rabid animal at the gastrocnemius area. The alternating magnetic flux emitted by the drum applicator (B) generates Eddy current within the targeted tissue. A towel (C) is placed between the applicator and the subject to remove any superficial water (e.g. sweat, moisture) which could concentrate electric current and produce excessive localised heat. This setting could replace Rabies Immunoglobulin (RIG) in Rabies post-exposure prophylaxis.

The capacitive DPDs generate an oscillating electrostatic field between condenser electrodes placed close to the skin with the electric current flowing through the in-between tissue (Fig. 2). The electric charges are more concentrated at the surface of the treated area compared to the inductive DPDs. A combination of inductive and capacitive DPDs could act synergistically to efficiently disseminate electrons both to the superficial and to the deeper layers of the treated tissue.

Previous studies

Electricity is known to adversely affect viruses. However, the direct application of electric voltage for therapeutic purposes on humans faces serious limitations. Human skin has tremendous impedance that may reach 100,000 ohms and can be penetrated only with high, lethal voltages when conventional electrodes are applied (e.g. naked wire). The current then flows at an unpredictable course through the path of the least impedance with a propensity to move along the periphery of human body (skin) rather than through the core (tissues) (Fish and Geddes 2009).

The virucidal effects of electric energy, mainly in the form of pulsed electric fields (PEF) of very high voltage for a very short time in food components and human-like cell substrates, have been previously described (Badylak et al. 1983, Mizuno et al. 1990, Lyman et al. 1996, Kumagai et al. 2011). In vitro studies reported that herpes simplex virus type 1 and adenovirus type 5 in mammal cell lines (Vero) were inactivated under the influence of electricity (Roohandeh and Bamdad 2011), whereas HIV was similarly neutralised in HeLa/ CD4(+) cells (MAGIC-5) (Kumagai et al. 2011). However, the non-enveloped enteric Rotavirus was found refractory to PEF (Khadre and Yousef 2002, Hirneisen et al. 2010). Researchers have demonstrated that virions have certain electrical properties, for example, resistance, capacitance, dielectric constant and manifest piezoelectric phenomena (MacCuspie et al. 2008, Yu 2012).

Recent studies have reported adverse effects of the electromagnetic radiation on SARS-COV-2; Sayidmarie et al. (2022) focused on identifying the ideal resonance for the maximum absorption of energy from the virion so as to neutralise the virus by overheating, whereas Cantu et al. (2023) applied high power electric fields for very short duration and reported reduction of survivability even in the abscence of thermal effects. However, these studies aimed for virus neutralisation in the environment and on inanimate objects such as surfaces. In a pioneering clinical trial, SARS-COV-2 patients were subjected to short wave radiation that resulted in reduction of inflammation, clinical improvement and shortening of hospitalisation; however, authors dismissed a direct effect of the intervention on the virus, based on the lack of change on the negative conversion rate (the duration from symptoms to a negative PCR test for viral RNA) (Huang et al. 2023).

Susceptibility of viruses to electricity

The amino acids are acidic, basic, non-polar (hydrophobic) or polar (Jaspard and Hunault 2014). Polarity is present at 10 of the 20 known proteinogenic, genetically encoded amino acids. Amongst the polar ones, three have basic side chains (R group) at neutral pH and, by binding protons, gain a positive charge (arginine, histidine, lysine), two have acidic side chains at neutral pH and, by offering protons, gain a negative charge (aspartic acid, glutamic acid) and five are non-basic and non-acidic, but have, at the side chain, electron pairs available for hydrogen bonding (asparagine, glutamine, serine, threonine tyrosine) (Alberts et al. 2002). At the molecular level, the polarity is affected by the acidity of the surrounding aqueous solution (pH) (Zhang et al. 2022) and may be localised to specific domains or subunits of the protein. The viral proteins may undergo changes due to physiological processes (e.g. cell adhesion, invasion, budding) potentially affecting their charge and polarity. Under a general configuration of a hydrophobic core surrounded by hydrophilic domains, a huge number of possible interactions amongst amino acids can occur which may affect the stereochemical structure (Kuntz and Kauzmann 1974, McColl et al. 2004, Romanenko et al. 2017). Viral proteins are of utmost importance for cell invasion and constitute an integral part of the replicatory machinery (Nagy and Pogany 2012).

Rabdoviridae specific polar profile

RABV M and G proteins play a crucial synergistic role in cell invasion, virion intracellular formation and the release from the host-cell of the new viral particles by budding (Mebatsion et al. 1999, Albertini et al. 2012). The glycoprotein G has in total 524 amino acids, distributed in four domains (Fernando et al. 2016). Alanine (Ala_{242}), aspartic acid (Asp_{255}), isoleucine (Ile_{268}) and arginine (Arg_{333}) seem to remain conserved in the glycoprotein G of RABV strains (Luo et al. 2012) and, amongst them, aspartic acid and arginine have negatively and positively charged R groups, respectively (Pawar et al. 2019, Zhang et al. 2022). Positively charged amino acids of the G protein of the Vesicular Stomatitis Virus, another member of *Rhabdoviridae*, interact electrostatically with negatively charged phospholipids of the cell membrane during the process of recognition and attachment to the host cell indicating the crucial role of electric phenomena to pathogenicity (Da Poian et al. 2005).

Impact

Common physiotherapeutic diathermy devices can be repurposed to neutralise RABV and replace the expensive and in short supply Rabies immunoglobulin. Apart from RABV, a wide range of pathogenic viruses may prove susceptible to the electric excitation induced by electromagnetism. The modality could be the precursor to a novel approach of combating viral infectious diseases by exploiting electric phenomena.

Implementation

A preliminary theoretical assessment revealed that the application of electromagnetic energy for the deactivation of Rabies virus is possible and commonly used RF diathermy devices may potentially replace the conventional RIG. The diathermy physiotherapy devices have clearance for therapeutic applications on human patients, have been used for decades in rehabilitation and can distribute electric energy at various tissue depth. However, the incapacitation of the targeted viruses by inflicting sufficient damage to the viral proteins is only a theoretical postulate. The outcome is an equation of the electric energy applied at molecular level, the susceptibility of the protein domains and the impact of the protein alteration to the viral pathogenetic machinery. The experimental testing of the modality on cell cultures and laboratory animals can elucidate how the applied electric field affects the virus. We propose the application of pulsed-mode, shortwave, induction-type diathermy or a combination of induction and capacity-type devices for even better distribution of the electric current. If the laboratory cannot handle RABV due to safety constraints, other members of the *Rhabdoviridae*, for example, *Vesiculovirus*, a virus of low zoonotic potential affecting mainly livestock (Liu et al. 2021), could be studied for gaining some insight as to the effectiveness of the design. A successful outcome may require the fine tuning of several variables, such as distance from the targeted area, voltage, current, frequency, waveform, frequency and duration of pulses, amount of energy and, possibly, a combination of inductive and capacitive DPDs. If the concept proves functional, protocols should be developed for the efficient use of DPDs as a replacement of RIG in the post-exposure prophylaxis scheme.

The benefits of the proposed modality as a RIG replacement include the significantly reduced expenses, the lack of anaphylaxis reaction, the equal protection against RABV and other Lyssaviruses, partially or not intercepted by the conventional PEP, such as the European Lyssaviruses (EBLV-1, EBLV-2), the Mokola virus (MOKV), the Lagos bat virus (LBV) and the West Caucasian bat virus (WCBV) (Weyer et al. 2008, Echevarría et al. 2019) and the application to anatomical sites inaccessible for RIG infiltration. Moreover, the emitted electromagnetic energy might intercept RABV even after the virus has gained access to the peripheral nerves, as in the case of delayed presentation of a bite victim. In this case, the virus location within the neural network could be assessed by a function of time and tissue migration speed. RF irradiation could also inactivate RABV in biological substances, for example, transplants.

Deleterious effects to other viral pathogens are possible as electrically sensitive proteinic components are not limited to RABV. Viruses localised in chronically-infected sites could be targeted with DPDs. For example, the dorsal ganglia and the liver could be targeted for Herpes simplex virus type 1 and Hepatitis C virus, respectively. The effectiveness of RF electric fields could be tried even in systemic viral infections via designs which deliver the emitted energy to large body areas or for prolonged periods. Enveloped viruses lack a durable protective capsid and might inherently be more vulnerable to the adverse effects of the electric current as some previous reports suggest that the non-enveloped viruses could be impervious to the flow of electric current (Khadre and Yousef 2002, Hirneisen et al. 2010).

Limitations

The use of RF diathermy devices should be avoided on oedematous tissues, pregnant or menstruating women or bacterial septic infections, for example, tuberculosis (Shah and Farrow 2007). Specific constraints apply for the recipients bearing metal or electronic implants (e.g. cardiac pacemaker), prone to thermal burns because of the increased conductivity or the risk or malfunction due to electromagnetic interference (Solberg et al. 2020). History should be carefully received from the patient for implanted metallic material or electronic devices. Safety concerns due to the exposure of the medical professionals and the recipients in stray electromagnetic radiation have been expressed (Draper et al. 2013). Harmuful effects on pregnancy and especially low birth weight have been demonstrated for health professionals using shortwave RF diathermy devices (Lerman et al. 2001). Others, however, did not identify adverse effects on pregnancy outcome associated with the exposure to shortwave RF, but reported a risk of miscarriage specifically related with the microwave RF (Ouellet-Hellstrom and Stewart 1993). According to Shields et al. (2004) and Almalty et al. (2023), the acknowledgement of the risks and potential hazards was suboptimal in physiotherapists working with RF devices, but the same authors also stated that the listed precautions and contra-indications were based on expert opinions rather than observational data. The operation of the RF shortwave/ microwave diathermy machines requires licensed health professionals or properly trained medical staff. However, if the modality was established as an acceptable alternative to RIG and standard protocols were devised, the use of DPDs would be expected to become more mainstream and accessible to the healthcare personnel. The budget required for the acquisition of an RF diathermy device, the maintenance costs and the technical specifications of the installation room should also be taken into consideration (Guirro et al. 2014).

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Ethics and security

N/A

Author contributions

Conceptualisation, methodology, writing-original draft preparation, revision, editing, visualisation, G.D.

Conflicts of interest

The authors have declared that no competing interests exist.

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