Menneskeskapte elektromagnetiske felt tvinger ioner til oscillering og fører til dysfunksjoner i spenningsstyrte ionekanaler, oksidativt stress og DNA-skade (gjennomgang)

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Sammendrag. Eksponering av dyr/prøver av biologisk materiale for menneskeskapte elektromagnetiske felt (EMF), spesielt i det ekstremt lave frekvensbåndet (ELF), og i mikrobølge-/radiofrekvensbåndet (RF) som alltid er kombinert med ELF, kan føre til DNA-skade. DNA-skade er forbundet med celledød, infertilitet og andre patologier, herunder kreft. ELF-eksponering fra kraftledninger og kompleks RF-eksponering fra trådløse kommunikasjonsantenner/-enheter er knyttet til økt kreftrisiko. Nesten alle menneskeskapte RF EMFer inneholder ELF-komponenter i form av modulasjon, pulsering og tilfeldig variasjon. Således er tilstedeværelsen av ELFer et fellestrekk ved nesten alle menneskeskapte EMFer, i tillegg til polarisering og koherens. Den foreliggende studien gjennomgår DNA-skaden og tilknyttede virkninger som påføres av menneskeskapte EMF. Gjennomgangen gir en omfattende beskrivelse av svingningsmekanismen som påtvinges ioner av polariserte/koherente EMFer og som forstyrrer åpning og lukking av spenningsstyrte ionekanaler i cellemembraner. Konsentrasjonene av ioner i cellene bestemmer cellens elektrokjemiske balanse og homeostase. Dysfunksjoner i ionekanaler forstyrrer disse. Den foreliggende studien viser hvordan dette kan føre til DNA-skade via overproduksjon av reaktive oksygenarter/frie radikaler. Det gis gjennom dette et fullstendig bilde av hvordan menneskeskapt EMF-eksponering helt klart kan føre til DNA-skade og tilknyttede patologier, herunder kreft. Dessuten framsettes den antakelsen at de ikke-termiske biologiske virkningene som tilskrives RF EMFer, i realiteten skyldes deres ELF-komponenter.

Originalens tittel: Human-made electromagnetic fields: Ion forced-oscillation and voltage-gated ion channel dysfunction, oxidative stress and DNA damage (Review)

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Forkortelser: DECT (digitally enhanced cordless telecommunications): digitalt forbedret trådløs telekommunikasjon ('snorløs fasttelefon'); ELF: ekstremt lav frekvens/ lavfrekvent; EMF: elektromagnetisk felt; MT: mobiltelefoni; OS: oksidativt stress; RF: radiofrekvens/radiofrekvent; ROS (reactive oxygen species): reaktive oksygenarter; ULF: ultralav frekvens/ultra lavfrekvent; VGIC (voltage-gated ion channel): spenningsstyrt ionekanal, dvs. med 'port' som åpnes/lukkes av spenningsforskjeller; VGCC (voltage-gated calcium channel): spenningsstyrt kalsiumkanal; TK (wireless communication): trådløs kommunikasjon; WiFi (wireless fidelity): (egentlig 'trådløs troverdighet') WiFi (en teknisk standard for trådløse nettverk); 2G/3G/4G/5G: andre/tredje/fjerde/ femte generasjon mobiltelefoni

Søkeord: EMF, ionesvingning, VGIC , frie radikaler, OS, ROS, DNA-skader, kreft

Innhold

1. Innledning

Eksperimentelle og epidemiologiske funn som knytter eksponering av levende organismer for ELF og komplekse menneskeskapte EMFer fra radiofrekvenser (RF) til genetisk skade, infertilitet og kreft. Det fins en mengde eksperimentelle funn som knytter så vel in vivo som in vitro eksponering av forsøksdyr og celler for ekstremt lavfrekvente (ELF) (3-3000 Hz) og for elektromagnetiske felt (EMF) med radiofrekvenser (RF)/mikrobølger (300 kHz-300 GHz), til genetiske skader/ endringer (blant annet DNA-skader, kromosomskader og mutasjoner), celledød og tilknyttede virkninger (1-4). De fleste funnene gjelder eksponering for EMF fra trådløs kommunikasjon (TK) [fra mobiltelefoner/antenner, snorløse fasttelefoner (blant andre DECT: digitally enhanced cordless telecommunications), trådløst internett (WiFi: trådløse lokalnett) og 'Bluetooth'-baserte trådløse tilknytninger,]. Disse kombinerer med nødvendighet bærefrekvenser for RF/mikrobølger med ELF-pulsing og modulering, og med tilfeldig ultralavfrekvent (ULF)

(0-3 Hz) variasjon av signalet. I dag inneholder nesten alle tekniske radiofrekvente EMFer (ikke bare slike RF som kommer fra trådløs kommunikasjon, men også fra blant annet radarer, radio- og fjernsynsantenner) ELF/ULF-komponenter i form av pulseringer som slås av/på, fra modulasjon og fra signalvariasjoner. Disse kalles vanligvis ganske enkelt 'RF', men egentlig er de kombinasjoner av radiofrekvenser (RF) og ekstra- og ultralave frekvenser (ELF/ULF) (4).

Antallet eksperimentelle laboratoriestudier som påviser genetisk skade og tilknyttede virkninger påført av EMF fra menneskeskapte ELF eller RF (kombinert med ELF), og da på en rekke organismer/celletyper under forskjellige eksperimentelle forhold, har økt raskt, særlig de siste årene (5-55).

Mange av de nevnte funnene har å gjøre med DNA-skade og påfølgende celledød i reproduktive celler hos forskjellige dyr, noe som fører til nedgang i reproduksjonen. Som rapportert gjennom forskjellige studier på en rekke dyr (25,30,31,36,40, 41,46), viser særlig virkningene av EMF fra pulserende trådløs kommunikasjon på DNA i reproduktive celler en markant likhet og de forklarer andre funn som forbinder EMF-eksponering for trådløs kommunikasjon med infertilitet blant insekter, fugler og pattedyr (herunder mennesker) (56–64), så vel som nedgang i fugle- og insektbestander (spesielt bier) i løpet av de siste 15 årene (65–69). En tydelig reduksjon i reproduksjon (redusert egglegging og fosterdød) etter eksponering for stråling fra mobiltelefoni (MT) ble observert å være likeartet hos bananfluer (30,40,57,58), kyllingegg (61), fugler (65-67), og bier (63). Lignende virkninger er rapportert for krypdyr (70,71), rotter (31,62) og menneskelig sædceller (redusert antall sædceller og redusert bevegelighet) (59,60). Disse markant like funnene i forskjellige organismer, som er gjort av forskjellige forskningsgrupper, kan forklares med den celledøden som er observert blant reproduktive celler etter DNA-skade, noe som er observert for bananfluers ovarieceller (30,40,41,46), menneskelige sædceller (36), og sædceller fra mus og rotter (25,31). At eksponering for EMF som er rene ELF, har ført til redusert reproduksjon etter DNA-skade og celledød blant reproduktive celler og til fosterdød, er også rapportert (4,9,14,22,47).

Samtidig kobler epidemiologiske/statistiske studier i økende grad menneskeskapt EMF-eksponering til helseproblemer, genetiske skader og kreft i menneskelige befolkningsgrupper. Mer spesifikt er ELF EMFer fra kraftledninger og høyspenttransformatorer (hovedsakelig 50–60 Hz pluss tilleggsfrekvenser på grunn av blant annet overharmoniske svingninger, støy og utladninger) knyttet til barneleukemi (72–82) ved magnetfeltintensiteter ned til 2 mG (0.2 μT) (76,82), og til avstander fra kraftledninger opp til 600 m (81), og til elektriske feltintensiteter ned til 10 V/m (78). RF-eksponering fra ulike antenner, som alltid inneholder ELF-komponenter, noe som særlig gjelder MT-antenner, er knyttet til ulike former for kreft. Hallberg og Johansson (83) fant en sammenheng mellom forekomst av hudkreft (melanom) hos mennesker og boligens eksponering for radiokringkastingsantenner, mens to nyere studier har funnet signifikant økt genetisk skade i perifere blodlymfocytter hos personer som bor i nærheten av MT-basestasjoner (84,85). I løpet av de siste 15 årene har epidemiologiske studier funnet en økende sammenheng mellom bruk av mobil- og trådløs telefon og hjernesvulster hos mennesker (86-98). I løpet av de siste 20 årene har statistiske studier dessuten funnet forbindelser mellom eksponering for MT-basestasjoner og -enheter og rapporterte symptomer på uvelvære omtalt som 'mikrobølgesyndrom' og 'el-overfølsomhet' (EHS). Symptomene omfatter hodepine, tretthet, søvnforstyrrelser m.m. (99-107). En høy prosentandel (~80 %) av pasienter som selv rapporterer seg som el-overfølsomme, ble nylig funnet å ha forhøyet nivå av oksidativt stress (OS) [økning internt i celler av frie radikaler/reaktive oksygenarter (ROS)] i sitt perifere blod (108).

En gjennomgang av studier som gjelder eksponering for komplekse RF-EMF med ELF-pulsering/modulering viste at 93% av disse studiene rapporterte at biologiske systemer ble påført overproduksjon av OS/ROS (109).

Påføring av kreft hos forsøksdyr ved langvarig mobiltelefoni (MT)-eksponering, som inneholder ELF-pulseringer, er også rapportert (110,111). En nylig studie under USAs nasjonale toksikologiske program (NTP) fant at rotter som var blitt eksponert i 2 år, 9 timer per dag, i nærfeltet av simulerte 2. generasjons (2G) eller 3.generasjons (3G) mobiltelefoni-stråling, utviklet hjernekreft (gliom) og hjertekreft (malignt schwannom), både ved lavere og høyere strålingsnivåer enn de grensene myndighetene aksepterer (112). Studien fant dessuten signifikant økt DNA-skade (trådbrudd) i hjernene til eksponerte dyr (113), noe som bekrefter at DNA-skade er nært knyttet til karsinogenese [utvikling av kreft, o.a.]. En italiensk studie av livslang eksponering av rotter i et simulert 2G mobiltelefoni-fjernfelt fant også at de ble påført schwannomer i hjertet og glia-svulster i hjernen, noe som bekrefter resultatene fra NTP-studien (114).

Disse funnene av kreftfremkallende egenskaper på dyr sammen med de epidemiologiske kreftfunnene på mennesker, DNA-skadene og OS-funnene og de negative virkningene på reproduksjonen på grunn av DNA-skade i kjønnscellene og fosterdød, peker i samme retning, som er at menneskeskapt EMF-eksponering forårsaker OS- og DNA-skader som kan føre til kreft, reproduksjonsnedgang og tilknyttede lidelser. Det er viktig å merke seg at eksponeringsnivåene i det store flertallet av alle de nevnte studiene (1-114) var betydelig under de offisielt aksepterte eksponeringsgrensene for ELF og RF EMF, som hva gjelder ELF er satt for å forhindre utladninger på mennesker [f.eks. støt og radarpulser, o.a.], og hva gjelder RF for å hindre oppvarming av levende vev (115,116).

Samtidig har flere andre studier rapportert at de ikke har funnet noen virkninger av ELF eller radiofrekvente EMF i noen av de nevnte endepunktene (1-4,47,57,115-124), og spesielt gjelder dette studier som har brukt eksponering for simulert mobiltelefoni/trådløs kommunikasjon (MT/TK) fra generatorer med ikke-varierende parametere (blant annet intensitet, frekvens og pulsing) og heller ingen modulasjon eller tilfeldig variasjon. Derimot ble det funnet virkninger i mer enn 95% av de studiene som brukte reell MT/TK-eksponering fra kommersielt tilgjengelige enheter (mobiltelefoner/trådløse telefoner og WiFi) med høy signalvariasjon (4,121,122). Selv når man ser bort fra om eksponeringen kom fra reelle eller simulerte kilder, finner flertallet av eksperimentelle studier (mer enn 70%) virkninger både i RF-båndet (som er kombinert med ELF) og i det rene ELF-båndet (4,109,123,124). I en nylig gjennomgang av 138 RF-studier med frekvenser >6 GHz som vurderte mulige virkninger fra 5. generasjons (5G) systemer for mobiltelefoni/trådløs kommunikasjon, som er under utrulling, undersøkte ikke forfatterne spesielt om det var ELF-komponenter i eksponeringen og eventuelt av hvilken type, eller om det fantes noen likheter uavhengig av bærefrekvensen mellom de signalene som ble produsert av generatorer i de undersøkte studiene, og de som inngår i 5G. Selv om de fleste av de gjennomgåtte studiene rapporterte virkninger, ble de i gjennomgangen kritisert for ikke å være 'uavhengig gjentatt' og for å bruke 'lavkvalitets metoder for vurdering og kontroll av eksponeringen' (125). Slik forsøkte forfatterne av gjennomgangen å nedgradere enhver rapportert virkning, samtidig som deres egen metodikk for gjennomgangen var mangelfull.

Under den økende vekten av vitenskapelige belegg har Det internasjonale kreftforskningsbyrået (IARC) nå for lengst

klassifisert både ELF og RF EMF som mulig kreftfremkallende for mennesker (gruppe 2B) (117-119). Basert på ytterligere vitenskapelig bevis etter IARC-klassifiseringen for RF EMF i 2011, har flere studier antydet at EMF fra radiofrekvenser/mobiltelefoni bør revurderes og klassifiseres som sannsynligvis kreftfremkallende (gruppe 2A) eller som kreftfremkallende (gruppe 1) for mennesker (92,97,126,127). Som allerede understreket, var ELF/ULF-komponentene til stede i de langt fleste studiene som ble betegnet som 'studier av RF'.

I de langt fleste studiene ovenfor (1-124) ble det rapportert virkninger som ble framkalt av ELF eller av EMF fra komplekse RF (som inneholder ELF), og som ikke ble ledsaget av noen oppvarming av betydning av det eksponerte levende vevet. Likefullt er det godt etablert at rene EMF fra RF/mikrobølger forårsaker oppvarming av eksponerte materialer (som f.eks. i mikrobølgeovner). Oppvarmingen fra mikrobølger blir betydelig ved høy styrke/intensitet ($\geq$0.1 mW/cm^2) [1 000 000 μW/m^2] og høy frekvens (i GHz-området) (128). Ut over dette er det knapt rapportert at rene RF EMF, som har svært begrenset teknisk bruk, framkaller ikke-termiske virkninger, og det er i slike tilfeller tvilsomt om det ble sørget nøye for at alle ELF ble utelukket (129).

DNA-skader og tilknyttede sykelige tilstander. Det er godt dokumentert at skade på DNA er forbundet med cellers aldring (cellealdring og tap av evne til å dele seg), celledød, nevrodegenerative sykdommer og aldring av organismen, og er hovedårsaken når kreft påføres av miljøstressorer (3,130-138). Hendelser som skader DNA inntreffer når som helst i cellene i enhver levende organisme og skyldes en rekke hendelser (så som eksponering for ultrafiolett stråling, naturlig radioaktivitet eller cytotoksiske kjemikalier), men for å beskytte mot dette har det utviklet seg effektive DNA-reparasjonsmekanismer. Som skade i DNA regnes enhver forandring i en nukleotidbase, deoksyribose, et brudd i en kovalent binding mellom deoksyribose og nukleotidbase, og et brudd i én eller begge båndene i en fosfodiesterbinding (3,130-139).

Kopiering av skadet (eller unøyaktig reparert) DNA kan inntreffe før reparasjon eller blokkering, og kan da føre til genmutasjoner, som så vil gi opphav til feilformede proteiner. Mutasjoner i onkogener, i svulstundertrykkende gener, i DNA-reparasjonsgener eller gener som kontrollerer cellesyklusen kan skape en klonet bestand av celler med en særegen evne til å formere seg. DNA-metylering, som kan hindre at DNA-reparasjonsgener får virke og syntese av forbundne proteiner, kan føre til unøyaktig ('feilutsatt') DNA-reparasjon. Mange slike hendelser, som kan akkumuleres over lang tid ved tilfeller der det skjer en vedvarende eksponering for kreftfremkallende stoffer, kan føre til genomisk ustabilitet og kreft (133,134,136, 139).

Når det genomiske DNAet til en celle er skadet av en ytre stressfaktor og skaden enten ikke kan repareres eller bare repareres unøyaktig, er følgende utfall mulige: i) Cellen dør (nekrose) eller ledes til selvmord (påført apoptose). Når dette gjelder celletyper som har evne til å formere seg, kompenserer organismen for tapet ved å skape nye celler, praktisk talt uten negative konsekvenser, bortsett fra energiforbruket, som kan føre til raskere aldring når slike hendelser forekommer hyppig. Når det gjelder celletyper som ikke har evne til å formere seg, slik som nerveceller og kondrocytter, vil tap av et betydelig antall celler sannsynligvis føre til at bestemte vev/organer ikke er i stand til å fungere normalt. Når det gjelder nerveceller, kan dette blant annet føre til nevrodegenerative sykdommer som Alzheimer og Parkinson, og til autoimmune lidelser. ii) Cellen dør ikke, men overlever med modifisert DNA. Når det gjelder somatiske celler som formerer seg, vil det modifiserte genomet reprodusere seg selv. Selv om organismen kanskje kan gjenkjenne slike mutante/muterte celler som fremmede og vil prøve å isolere dem og fjerne dem, streber de etter å overleve og kan begynne å spre seg ukontrollert. Da setter de i gang kreft. Når det gjelder reproduktive celler (oocytter og spermatocytter), kan dette føre til nye muterte organismer som kan være problematiske på mange måter, eller kan være utsatt for kreft. I begge tilfeller (både somatiske og reproduktive celler) er cellealdring en alternativ utviklingsvei for å eliminere overlevende genetisk defekte celler. Celler med uopprettelig skadet genomisk DNA vil således lede til cellealdring, celledød, kreft, eller mutert avkom, alt etter celletype og spesifikke biologiske/miljømessige forhold (3,4,122,130-132,135-137).

Tiden det tar før kreft utvikles etter uopprettelig DNA-skade (latensperioden) kan være flere år, avhengig av organismen og krefttypen. Latensperioden for gliomer (en type hjernekreft) er vanligvis >20 år hos mennesker (140). Dette forklarer sannsynligvis hvorfor epidemiologiske studier først i løpet av de siste ~15 årene har begynt å påvise en sammenheng mellom bruk av mobiltelefon og kreft (86), mens det lenge før er funnet indikasjoner på kreft fra kraftledninger, som jo er flere tiår eldre enn mobiltelefoni/trådløs kommunikasjon (72).

Hensikten med den foreliggende studien. Som tidligere nevnt forbinder et økende antall eksperimentelle og epidemiologiske/statistiske funn menneskeskapt EMF-eksponering med genetisk skade og kreft, noe som innebærer brudd på kjemiske/elektroniske bindinger i molekyler/atomer, med andre ord ionisering. De menneskeskapte EMFene med frekvenser opp til den nedre grensen for infrarødt (0-3·10^{11} Hz) som drøftes i denne studien, kan ikke forårsake ionisering direkte, bortsett fra ved svært sterke feltintensiteter ($\geq$10^6 V/m) (141,142). Slike feltintensiteter forekommer sjelden i miljøet, bortsett fra ved atmosfæriske utladninger (lyn) eller svært nær høyspentledninger og transformatorer. Spørsmålet er derfor hvordan menneskeskapte EMF ved intensiteter man finner i miljøet, er i stand til å skade DNA og andre biologiske molekyler. Det er åpenbart at de evner å bryte kjemiske bindinger indirekte gjennom virkningen(e) fra én eller flere innledende biofysiske mekanismer, med påfølgende igangsettelse av biokjemiske prosesser inne i cellene.

Synlig og infrarødt naturlig lys kan ikke bryte kjemiske bindinger, selv om de eksponerer oss for høyere frekvenser og strålingsintensiteter enn menneskeskapte EMF i dagliglivet (143). I motsetning til naturlig infrarødt og synlig lys, må de menneskeskapte EMFene ha en unik egenskap som gjør dem i stand til å fremkalle skadelige biologiske/helsevirkninger og ionisering. Denne unike egenskapen er at menneskeskapte elektromagnetiske felt/stråling er fullstendig polariserte og koherente, noe som betyr at de, uavhengig av strålingsintensiteten, har netto elektriske og magnetiske felt som utøver krefter på enhver elektrisk ladet (eller polær) partikkel/molekyl, så som oppløste/frie ioner og ladede makromolekyler, som fins i ethvert biologisk system (143).

Formålet med den foreliggende studien er å legge fram en slik realistisk innledende biofysisk mekanisme for polariserte og koherente EMF som ved intensiteter som er relevante for dem vi finner i miljøet, svekker cellers funksjoner og setter i gang plausible biokjemiske prosesser internt i cellene, som så fører til

genetisk skade og at kreft oppstår [karsinogenese], i samsvar med det som er rapportert i de nevnte studiene.

2. Biofysisk påvirkning fra polariserte/koherente EMF som resulterer i dysfunksjoner i spenningsstyrte ionekanaler (VGIC) og forstyrrelser av cellers elektrokjemiske balanse

Det er påvist at selv ved svært lave feltintensiteter kan polariserte/koherente EMF i ULF- og ELF-frekvensbåndene forårsake uregelmessig åpning og lukking av elektrisk følsomme ionekanaler, såkalte VGICer [Voltage-Gated Ion Channels], i cellemembranene ved hjelp av 'mekanismen for ionefremtvunget oscillering' (143 -146), med påfølgende forstyrrelse av cellens elektrokjemiske balanse (som er den elektriske og osmotiske likevekten som i henhold til Nernst-ligningen vedlikeholdes på tvers av alle cellemembraner ved hjelp av spesifikke konsentrasjoner av de enkelte oppløste/frie ionene) (144,147,148). Siden det, som forklart, også finnes ELF/ULF-komponenter i de komplekse EMFene fra mobiltelefoni/trådløs kommunikasjon, forklarer denne mekanismen de biologiske virkningene av det store flertallet av menneskeskapte (polariserte og koherente) EMF, slik det vil bli grundig gjennomgått nedenfor.

Mekanismen er basert på gitte molekylære/fysiske forhold, og på kreftene som virker på mobile ioner i nærheten av spenningssensorene til VGICer når de påføres et polarisert oscillerende EMF. Det oscillerende feltet vil tvinge frie ioner til å oscillere i parallelle plan og i fase med feltet. Denne koordinerte bevegelsen av elektrisk ladede partikler utøver elektriske krefter på spenningssensorene, i likhet med de kreftene som utøves på dem av endringer i det elektriske feltet over membranen [dvs, mellom membranens utside og innside, o.a.], og som er kjent for fysiologisk å åpne og lukke disse kanalene. Dermed blir kanalene åpnet/lukket uregelmessig av det påførte EMF. Kreftene er proporsjonale med amplituden til den tvungne oscilleringen, og dermed er amplituden et direkte mål på den biologiske påvirkningen til det påførte EMFet. Det er vist at amplituden ([og dermed] den biologiske aktiviteten) er proporsjonal med intensiteten til EMFet, omvendt proporsjonal med EMFets frekvens, og at den dobles ved pulsede EMF. At den foreslåtte mekanismen er gyldig, er blitt verifisert ved numerisk testing, mens andre tidligere foreslåtte mekanismer ikke har klart å bestå den samme testen (149,150). Gjentatt uregelmessig åpning og lukking av spenningsfølsomme ionekanaler forstyrrer cellers elektrokjemiske balanse og homeostase (147,148), noe som fører til overproduksjon av ROS/frie radikaler som beskrevet nedenfor.

Det er kjent fra en stor mengde data fra eksperimenter at de mest bioaktive EMFene er de lavere frekvensene (ELF/ULF). I tallrike tilfeller der det er funnet biologiske virkninger påført av EMF fra komplekse RF modulert med ELF, har man funnet at modulasjonen (ELF), og ikke bærefrekvensen (RF), er ansvarlig for de registrerte virkningene. I tillegg er det gjentatte ganger blitt funnet at pulserende RF-EMF med pulsrepetisjon som har ELF-hastigheter, er biologisk mer aktive enn kontinuerlige (ikke-pulserende) felt, selv når de er identiske på andre parametere (1-5,44,45,47,151-159). Disse funnene er i fullt samsvar med den beskrevne mekanismen.

Biologiske molekyler av avgjørende betydning, som blant annet ioner, vannmolekyler, proteiner, nukleinsyrer og lipider, er enten polære [dvs. har ulik ladning i ulike deler av molekylet, o.a.] eller har en netto elektrisk ladning (147,148). Det elektriske nettofeltet fra et uendelig antall individuelle elektriske pulser med tilfeldig polarisering og/eller tilfeldig fase (som f.eks. fotoner i naturlig lys) tenderer til enhver tid mot null (og det samme er tilfellet for det netto magnetiske feltet).

$$\lim_{n\to\infty}\sum_{i=1}^{n}\vec{E}_i = \quad \vec{E}_1+\vec{E}_2+\vec{E}_3+\ldots+\vec{E}_n = 0 \tag{1}$$

Ikke-polariserte/ikke-koherente EMF (som f.eks. lys og kosmiske mikrobølger) kan dermed ikke, uansett strålingsintensitet, forårsake noen parallell/koherent oscillering av ladede/polære molekyler (143). Derimot tvinger polariserte og koherente (menneskeskapte) oscillerende EMF alle ladede/polære molekyler i biologisk vev til å oscillere i plan som er parallelle med deres polarisering og i fase med dem. Dette er avgjørende viktig for å forstå den beskrevne mekanismen. Den påtvungne oscilleringen vil virke mest intenst på de frie ionene, som er de minste ladede partiklene og er oppløste i høye konsentrasjoner i de vandige løsningene i alle levende celler/vev, både de cytosoliske [inne i cellene, o.a.] og i de ekstracellulære [utenfor cellene, o.a.], og som kontrollerer praktisk talt alle cellulære/biologiske funksjoner (147,148).

Alle molekyler beveger seg på grunn av termisk energi tilfeldig og med langt større hastigheter/omplasseringer, men disse bevegelsene har ingen annen biologisk virkning enn å øke vevstemperaturen. Derimot kan en polarisert og koherent oscillering med langt lavere energi enn den gjennomsnittlige termiske molekylære energien, sette i gang biologiske virkninger (143-145).

De fleste kation-kanalene (bl.a. Ca^{2+}, K^+, Na^+ og H^+) i membranene til alle dyreceller er spenningsstyrte (147,148). Disse ionekanalene skifter mellom åpen og lukket tilstand når den elektrostatiske kraften på spenningssensorene deres overstiger en kritisk verdi på grunn av spenningsendringer over membranen. Spenningssensorene er fire symmetrisk arrangerte, positivt ladede α-helikser som går gjennom membranen, hver med navnet S4. S4-heliksene inntar den fjerde posisjonen i en gruppe på 6 parallelle α-helikser (S1-S6). Kanalen består av fire like slike grupper i symmetriske posisjoner rundt kanalens pore. S5-S6-heliksene til de fire gruppene danner poreveggene (147,148). For å være mer nøyaktig, er sensorene positive Lys- og Arg-aminosyrer i S4-heliksene. Normalt trengs det endringer i spenningen over membranen i størrelsesorden ~30 mV for å styre spenningsfølsomme kanaler (endre deres status fra åpnet til lukket og omvendt) (160,161). Av S1-S4 α-heliksene er S4-heliksene nærmest S5-S6-heliksene, som er de poredannende, og de er plassert <1 nm i avstand fra poren (162,163). I tillegg til de ionene som til ethvert tidspunkt måtte passere gjennom poren eller befinner seg like utenfor porten og er klare til å passere, kan også flere andre ioner til ethvert tidspunkt samtidig påvirke en S4-sensor fra en avstand av i størrelsesorden 1 nm, ettersom noen flere ioner er bundet til bestemte ionebindingssteder nær porene (f.eks. er det tre i kaliumkanaler) (164,165). Også kanaler som styres av spenninger i protoner, noe som er undersøkt først ganske nylig, inneholder S4 helikser som går gjennom membranen, med ladede Arg-rester som spenningssensorer, og likner på de metalliske kation-kanalene (166,167).

La oss vurdere fire identiske frie ioner som er i avstander på i størrelsesorden 1 nm fra kanalsensorene (S4) og et eksternt påført oscillerende EMF. Den gjennomsnittlige elektriske (og magnetiske) kraften som påvirker hvert ion og er forårsaket av det som måtte finnes av ikke-polariserte EMF, er null (Lign. 1). Derimot er kraften som er forårsaket av et polarisert felt med en elektrisk komponent E, $F = Ezq_e$ (der zq_e er ionets elektriske ladning).

I det vanligste og enkleste tilfellet, der vi har et felt fra sinusformet elektrisk vekselstrøm, $E=E_o \sin\omega t$, er ligningen for bevegelsen (tvungen oscillering) til et fritt ion som følger (143-146):

$$m_i \frac{d^2r}{dt^2} + \beta \frac{dr}{dt} + m_i \omega_o^2 r = E_o z q_e \sin\omega t \quad (2)$$

der m_i er ionets masse, r er forskyvningen av ionet på grunn av den påtvungne oscilleringen, z er ionets valens (z =1 for K^+-, Na^+-, eller z =2 for Ca^{2+}-ioner), q_e =1.6·10^{-19}C er den elementære ladningen, β er dempningskoeffisienten (som er innenfor kanalene $\beta = \frac{E_m z q_e}{u_o} \cong$ 6.4z·10^{-12} kg/s, med E_m (~10^7 V/m) til det transmembrane elektriske feltet, og u_o = 0.25 m/s er hastigheten til ionet gjennom en åpen kanal beregnet utfra målinger av ionestrømmer gjennom kanaler gjort med *patch-clamp* [ørsmå klemmer som brukes til å måle spenninger direkte på cellenivå, o.a.]). $\omega_o = 2\pi v_o$ (v_o ionets oscilleringsegenfrekvens er her forutsatt å være lik de spontane intracellulære ioniske oscilleringsfrekvensene, som er målt til å være i størrelsesorden 0.1 Hz), $\omega=2\pi v$ (der v er frekvensen til det påførte feltet) og E_o er amplituden til det påførte oscillerende feltet ved den gitte intensiteten. Detaljerte beregninger av parameterne er gitt i Panagopoulos *et al* 2000 (144).

Den høyre delen av Lign. 2 er kraften som utøves på ionet på grunn av det påførte E-feltet. Det første leddet i venstre del er resultantkraften på ionet, det andre leddet er en dempende kraft og det tredje leddet ($m_i \omega_o^2 r$) er en tilbakestillingskraft som utøves av mediet (144,145). Mens et oscillerende ion nær S4-sensorene utøver krefter som bidrar til å endre om kanalen står åpen eller lukket, mottar porten null kraft i motsatt retning, ettersom S4-ladningene er paret med motsatte ladninger fra kanalens tilstøtende helikser (148). Lign. 2 er en annenordens lineær differensialligning med konstante koeffisienter, som er løsbar når vi kjenner verdiene til de forskjellige parameterne.

Den generelle løsningen av Lign. 2 (144) er:

$$r = \frac{E_o z q_e}{\beta\omega} \cos\omega t + \frac{E_o z q_e}{\beta\omega} \quad (3)$$

Konstantleddet $\frac{E_o z q_e}{\beta\omega}$ i løsningen beskriver en konstant forflytning av ionet og har ingen innvirkning på det oscillerende leddet $\frac{E_o z q_e}{\beta\omega} \cos\omega t$. Denne konstante forflytningen innebærer et hopp i hele oscilleringen med en avstand lik amplituden, med andre ord dobler den oscilleringens amplitude $\frac{E_o z q_e}{\beta\omega}$ i det øyeblikket feltet påføres eller avbrytes. For pulsede felt (som det store flertallet av menneskeskapte komplekse RF/mikrobølgede EMF er, spesielt de som brukes i moderne trådløs kommunikasjon), skjer denne avbrytelsen/repetisjonen kontinuerlig ved hver eneste puls som gjentas. Derfor kan pulsede felt forutsies å være dobbelt så biologisk aktive som kontinuerlige/ikke-pulsede felt med de ellers samme parameterne, og dette forklarer en mengde ulike eksperimentelle funn som viser økt biologisk aktivitet fra pulsede, sammenlignet med ikke-pulsede, RF-EMF, mens disse tidligere var uforklarte (44,45,154,155,157–159).

Ser vi bort fra konstantleddet i Lign. 3, er amplituden til den tvungne oscilleringen:

$$A = \frac{E_o z q_e}{\beta\omega} \quad (4)$$

Et oscillerende ion med ladning zq_e (som vil ha en bevegelse som beskrevet av Lign. 3) nær S4-heliksene til en spenningsstyrt kanal, utøver en kraft F på den faktiske ladningen q til hver S4, slik som beskrevet av Coulombs lov: $F = \frac{1}{4\pi\varepsilon\varepsilon_o} \cdot \frac{q \cdot z q_e}{r^2}$, ($r$ er her avstanden til den oscillerende ion fra S4). Ionet, som er fortrengt av dr under sin oscillering, påfører en ekstra kraft dF på hver S4-sensor:

$$dF = -\frac{q \cdot z q_e}{2\pi\varepsilon\varepsilon_o r^3} dr \quad (5)$$

Mens kraften i tilfelle av en tilfeldig/kaotisk bevegelse av ionet på grunn av f.eks. termisk bevegelse, vil være $\lim \sum d\vec{F} = 0$ og $\lim \sum d\vec{F} = 0$, vil den samlede kraften på hver S4 fra alle fire ioner når det skjer koordinert polarisert og koherent tvungen oscillering, være:

$$4dF = -2\frac{q \cdot z q_e}{\pi\varepsilon\varepsilon_o r^3} dr \quad (6)$$

Den effektive ladningen for hvert S4-domene er funnet å være: q=1.7q_e (161). Kraften på denne ladningen som utøves av en endring på 30 mV i spenningen over membranen, og som normalt kreves for å endre om kanalen er åpen/lukket, er beregnet til å være (144): dF = 8.16·10^{-13}N.

Den forskyvningen i kanalen av ett enkelt ion med enkel valens som tilsvarer denne minimumskraften, er i henhold til Lign. 5 (for z=1, $e \cong 4$, og r ~1 nm): dr=4·10^{-12} m.

Den dielektriske konstanten i proteiner er betydelig lavere enn i de vandige løsningene (4/80), og ionekonsentrasjonen i cellene er i størrelsesorden 1 ion per nm^3 (144,147,148).

For 4 ioner med enkel valens som oscillerer i parallelle plan og i fase med et polarisert (og koherent) oscillerende felt de er påført, reduseres minimumsforskyvningen (i henhold til Lign. 6) til: dr=10^{-12} m. Den tilsvarende nødvendige forflytningen for ioner som er utenfor kanalen vil være omtrent 20 ganger større på grunn av den høyere dielektriske konstanten i de vandige løsningene.

Dermed har vi nådd fram til et avgjørende funn: Ethvert eksternt polarisert og koherent oscillerende EMF (som alle tekniske/menneskeskapte EMF er) som er i stand til å tvinge frie ioner til å oscillere med amplitude

$$\frac{E_o z q_e}{\beta\omega} \geq 10^{-12} \text{ m} \quad (7)$$

er i stand til å forstyrre VGICer, dvs. åpne/lukke porter i celle-membraner «utenom tur». For z=1 (f.eks. K^+-ioner), og erstatter vi q_e, β med deres verdier i Betingelse 7 får vi:

$E_o \geq 0.25 v \cdot 10^{-3}$ (8) (v i Hz, E_o i V/m)

For kationer med dobbel valens (z=2) (f.eks. Ca^{2+}) blir betingelsen:

$E_o \geq 1.2 v \cdot 10^{-4}$ (9) (v i Hz, E_o i V/m)

Videre er høyre del av Betingelse 9 å dele med 2 for situasjoner med pulsede felt (slike som alle felt fra mobiltelefoni/ trådløs kommunikasjon), og blir da:

$E_o \geq 0.6 v \cdot 10^{-4}$ (10) (v i Hz, E_o i V/m)

Det er tydelig at amplituden til den påtvungne oscilleringen gitt av Lign. 4 er den kritiske parameteren for å bestemme hvilken evne et polarisert/koherent EMF har til å indusere biologiske/helsemessige virkninger. Vi skal kalle det "EMFets bioaktivitet" eller "EMF-bioaktivitet". Og dermed følger:

$$\text{EMF-Bioactivity} = \frac{E_o z q_e}{\beta \omega} = k \cdot \frac{E_o}{v} \quad (11)$$

der $k = \frac{z q_e}{2\pi\beta} = \frac{u_o}{2\pi E_m} \cong 4 \cdot 10^{-9}$ C·s/kg er en konstant mengde (som er avhengig av membranens elektriske felt E_m og ionets hastighet gjennom en åpen kanal u_o), E_o er amplituden ved den gitte intensiteten og v er frekvensen til det påførte elektriske feltet. Vi skal kalle k for 'bioaktivitetskonstanten'.

Vi får dermed det høyst rimelige og elegante resultat at den biologiske aktiviteten fra et polarisert oscillerende EMF er proporsjonal med dets maksimale intensitet (E_o) og omvendt proporsjonal med dets frekvens (v), noe som betyr at felt med lavere frekvens kan forutsies å være mer biologisk aktive enn høyere frekvenser med samme intensitet og bølgeform. Selv om dette resultatet ble oppnådd med tanke på det mest vanlige/enkle tilfellet med harmonisk oscillerende polariserte EMF, er det åpenbart at også ikke-harmonisk oscillerende polariserte felt kan beskrives tilnærmelsesvis med tanke på deres biologiske påvirkning ved hjelp av Lign. 11.

For pulsede EMF med bærebølger som svinger harmonisk, dobles amplituden, og det samme gjør den biologiske aktiviteten:

$$\text{Pulsed EMF-Bioactivity} = 2k \cdot \frac{E_o}{v} \quad (12)$$

Hvis vi i Lign. 2 erstatter den elektriske kraften $F_E = E z q_e$ med en magnetisk kraft, forklarer den samme mekanismen også den biologiske virkningen fra polariserte oscillerende magnetfelt, så

$F_B = B \text{ u } z q_e$ (13)

og utøves på et ion med ladning zq_e, som beveger seg med hastigheten u vertikalt på retningen til et magnetfelt med intensitet B. (I dette tilfellet er den magnetiske kraften maksimal.) I det enkleste (og mest vanlige) tilfellet med et vekslende magnetfelt $B = B_o \sin\omega t$ med intensiteten gitt som amplitude B_o og basert på samme resonnement som tidligere, oppnås det tilsvarende betingelser for biologisk aktivitet fra et oscillerende magnetfelt.

For et ion med enkel valens som beveger seg gjennom en åpen kanal vertikalt på retningen til det påførte magnetfeltet med $u = u_o = 0.25$ m/s (hastigheten beregnet for ioner som beveger seg gjennom en åpen kanal) (144) og for tilfellet med et kontinuerlig oscillerende magnetfelt, er den tilsvarende tilstanden for biologisk virkning:

$\frac{B_o u_o q_e}{\beta \omega} \geq 4 \times 10^{-12}$ m (14) (ω angitt i rad/s, u i m/s, B_o i T)

Utfra denne kan vi utlede:

$B_o \geq 4 \cdot 10^{-3} v$ (15) (v i Hz, B_o i T), og

$B_o \geq 4 \cdot 10^{3} v$ (16) (v i Hz, B_o i μT)

For ioner med dobbel valens deles høyre del av Betingelse 16 med 2:

$B_o \geq 2 \cdot 10^{3} v$ (17) (v i Hz, B_o i μT)

For ioner med dobbel valens og pulserende magnetfelt deles høyre del av Betingelse 17 videre med 2, og betingelsen for biologisk virkning blir da:

$B_o \geq 10^{3} v$ (18) (v i Hz, B_o i μT)

Det skal bemerkes at i tillegg til det som er akseptert som ionets driftshastighet i starten gjennom kanalen ($u_o = 0.25$ m/s), vil ionet få en ekstra hastighet dr/dt på grunn av den tvungne oscilleringen. Fra Lign. 3, får vi følgende:

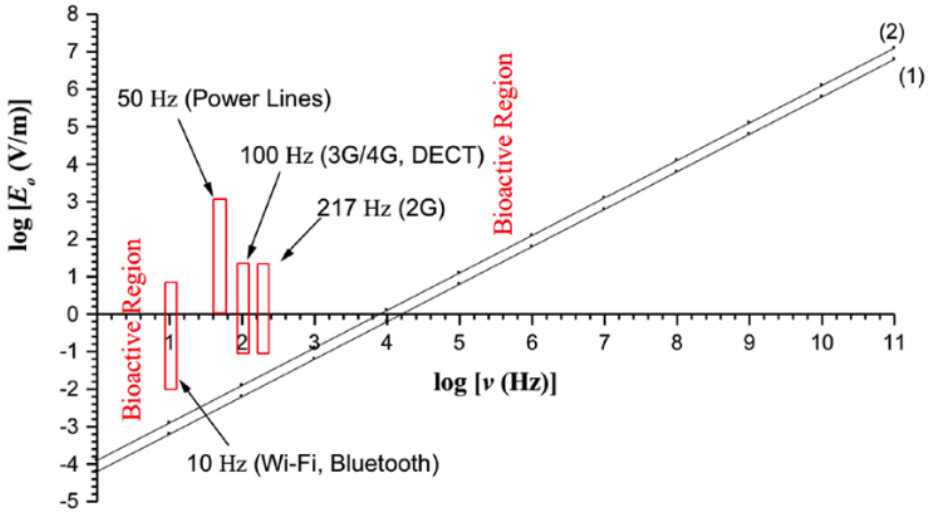
$$\frac{dr}{dt} = - \frac{E_o z q_e}{\beta} \sin \omega t \quad (19)$$

(eller det tilsvarende $\frac{dr}{dt} = - \frac{B_o u_o z q_e}{\beta} \sin \omega t$ for et sinusformet magnetfelt).

Den tilsvarende magnetiske kraften på grunn av denne tilleggshastigheten, Bzq_e (dr/dt), er ubetydelig (mer enn 10^8 ganger mindre) sammenlignet med dempingskraften $\beta(dr/dt)$, og derfor tas den ikke i betraktning i Lign. 2.

Denne tilleggshastighetens maksimum ($\frac{E_o z q_e}{\beta}$ or $\frac{B_o u_o z q_e}{\beta}$) er uavhengig av feltets frekvens (ω) og er ved vanlige feltintensiteter langt lavere enn ionehastigheten gjennom en åpen kanal (u_o=0.25 m/s), som igjen er mer enn 10^3 ganger mindre enn den gjennomsnittlige hastigheten som ionet må ha for å ha termisk virkning u_{kT} (168). Dermed fører ikke den beskrevne ionesvingningen til økt vevstemperatur. Denne mekanismen er derfor 'ikke-termisk', i motsetning til den velkjente oppvarmingsevnen til mikrobølger med høy intensitet (128). Den ikke-termiske naturen til biologiske virkninger fra menneskeskapte EMF, herunder de virkningene som følger av modulerte/pulserende RF/mikrobølger med lav intensitet, i motsetning til virkningene fra mikrobølger med høy intensitet, er også blitt drøftet i tidligere studier (169,170).

Denne teorien tillater oss å gjøre enkelte spådommer om den biologiske aktiviteten til visse menneskeskapte EMF som er tilstede i utstrakt grad i det moderne miljøet: For de sinusformede vekslende (kontinuerlige) 50 Hz E- og B-feltene fra høyspentledninger med intensiteter i størrelsesorden E~10 kV/m og B~0.1-1 G (dvs. ~10-100 μT) og ved nære avstander (10-20 m) fra slike linjer, gir betingelsene 9 og 17 for kationer med dobbel valens (f.eks. Ca^{2+}) disse resultatene: $E_o \geq 6 \cdot 10^{-3}$ V/m eller $E_o \geq 6$ mV/m (som overoppfylles med mer enn 10^6 ganger), og $B_o \geq 10^5$ μT, som ikke oppfylles. Dette viser at de registrerte virkningene fra høyspentledninger skyldes den elektriske, snarere enn den magnetiske, komponenten i det resulterende EMF, i motsetning til hva som vanligvis antas. Det følger at den elektriske komponenten i EMF fra kraftledninger så absolutt er i stand til å gi biologiske virkninger i levende organismer gjennom den mekanismen som er redegjort for her, selv ved



Figur 1. Diagram over E-felts biologiske aktivitet. Diagrammet viser de biologisk aktive kombinasjonene av elektrisk feltintensitet og frekvens som er i stand til å påføre biologiske/helsevirkninger gjennom mekanismen for ionesvingninger som fører til dysfunksjon av spenningsstyrte ionekanaler i celler. De elektriske ELF-feltene til kraftlinjer, 2G/3G/4G MT, DECT, WiFi og Bluetooth er innenfor den biologisk aktive regionen (over linjene 1 og 2). Linje 1 refererer til pulsede felt, slik som ELF-pulsingene i TK EMF (betingelse 10), mens linje 2 refererer til kontinuerlige (ikke-pulsede) felt som de fra kraftledninger (betingelse 9).

intensiteter ned til 1-10 V/m, som finnes i de fleste hjem og på de fleste arbeidsplasser.

For de pulserende ELF *E*- og *B* -feltene til EMF fra mobiltelefoni/trådløs kommunikasjon som er pulserende med en repetisjonshyppighet på ~100 Hz (3G/4G mobiltelefoni, DECT), der *E* ~10 V/m og *B* ~1 mG (eller ~0,1 μT) (30,40, 54,55), gir Betingelsene 10 og 18 for biologisk aktivitet henholdsvis: $E_o \geq 6 \cdot 10^{-3}$ V/m og $E_o \geq 6$ mV/m, som innfris i størrelsesorden mer enn 10^3 ganger, og $B_o \geq 10^5$ μT, som ikke innfris ved direkte innvirkning, men kan innfris av det magnetisk påførte elektriske feltet, som er betydelig i dette tilfellet på grunn av de korte stige- og falltidene til pulsene (143). Lignende resultater oppnås for de pulserende E/B-feltene til 2G mobiltelefoni på 217 Hz (30,40).

For trådløse WiFi- og Bluetooth-forbindelser med en pulsfrekvens på ~10 Hz, med *E*~1 V/m og *B*~0,1 mG (dvs. ~0.01 μT) (171), gir betingelsene 10 og 18 for biologisk aktivitet henholdsvis: $E_o \geq 0.6 \cdot 10^{-3}$ V/m og $E_o \geq 0.6$ mV/m, som oppfyller betingelsene med mer enn 10^3 ganger, og $B_o \geq 10^4$ μT, som ikke oppfyller betingelsene for direkte påvirkning.

De forannevnte numeriske eksemplene viser at det er det elektriske feltet som ser ut til å være den bioaktive komponenten i et EMF, altså ikke det magnetiske feltet, i motsetning til det som har vært antatt tidligere av aktører innen helse (117). Ved ELF-pulser i signaler i mobiltelefoni med korte stige-/falltider kan også det magnetisk påførte elektriske feltet være bioaktivt (143).

Betingelsene 9 og 10 for biologisk aktivitet for henholdsvis kontinuerlige og pulserende elektriske felt er avbildet i Fig. 1. Området over linje 1 (herunder linjen) representerer de biologisk aktive kombinasjonene av intensitetsamplitude (E_o) og frekvens (ν) for pulsede felt, og over linje 2 (inkludert linjen) det tilsvarende for kontinuerlige felt. De elektriske ELF-feltene fra kraftledninger, fra 2G/3G/4G mobiltelefoni, DECT, WiFi og fra 'Bluetooth' ligger innenfor den bioaktive regionen som den ovenfor framlagte teorien forutsier.

3. Biokjemiske prosesser som aktiveres av uregelmessig styring av VGICer, og som fører til DNA-skade

Forstyrret åpning/lukking av ionekanaler og ROS. Forstyrret åpning/lukking av VGICer på grunn av oscillerende polariserte og koherente ELF-EMF, slik som er beskrevet her [og opprinnelig i (143-146)], er blitt verifisert eksperimentelt for kalsium- (Ca^{2+}), kalium- (K^+) og natrium- (Na^+) VGICer (172-174). Slik åpning/lukking kan endre ioniske konsentrasjoner i cellen, forstyrre den elektrokjemiske balansen i cellen og føre til DNA-skade gjennom overproduksjon av OS/ROS (175-179).

De fleste ROS er frie radikaler. Frie radikaler er svært ustabile molekyler som inneholder et uparet elektron, som betegnes med en prikk (·), og de har en enormt sterk tendens til å reagere kjemisk med omgivende molekyler og/eller med hverandre for å få koblet på det uparede elektronet og dermed bli stabile. Dette er grunnen til at de har ekstremt korte levetider. De fleste ROS reagerer raskt med omgivende biomolekyler og forårsaker kjemiske endringer (180). Overproduksjon av ROS i levende celler på grunn av EMF-eksponering er blitt pålitelig dokumentert, med to viktige ROS funnet etter EMF-eksponering. Disse er superoksid-anion ($O^{2\bullet-}$) og nitrogenoksid ($NO^\bullet$) (109). Disse kan føre til dannelse av henholdsvis hydroksylradikal ($OH^\bullet$) og peroksynitritt ($ONOO^-$), som begge er ROS som er svært reaktive med biologiske molekyler og spesielt med DNA, noe som vil bli drøftet i det følgende. $ONOO^-$ kan interagere direkte med DNA, ettersom det på samme måte med $NO^\bullet$ kan spre seg til overalt i cellen (181). Superoksid-anion-radikalet ($O_2^{\bullet-}$) katalyseres av superoksid-dismutase-enzymer i cytosolet eller i mitokondriene og omdannes til hydrogenperoksid (H_2O_2) (109,182):

$$2O_2^{\bullet-} + 2H^+ \rightarrow H_2O_2 + O_2 \quad (20)$$

H_2O_2 er et avgjørende molekyl når det gjelder oksidativ skade ettersom det kan bevege seg til et hvilket som helst sted i cellen (herunder kjernen), hvor det kan omdannes til det

særdeles potente $OH^{\bullet}$, som kan skade ethvert biologisk molekyl, herunder DNA (183-187).

DNA-skade som er forårsaket av ROS og fører til mutasjoner og sykdom, er godt studert (188,189). I en gjennomgang av studier av biologiske virkninger fra EMF med bruk av kalsium-kanalblokkere, påpekte Pall (190) en sammenheng mellom spenningsstyrte kalsiumkanaler (VGCCer) og overproduksjon av $NO^{\bullet}/ONOO^{-}$. Dette bekreftet tidligere observasjoner av virkninger på intracellulære kalsiumkonsentrasjoner påført av EMF, og den unike rollen som VGCCene har (1,151-153,191, 192).

Det er kjent at redoksstatusen internt i cellen kan aktivere Ca^{2+}-, Na^{+}- og K^{+}-kanaler for å gjeninnføre homeostase (178), og omvendt bestemmer aktivering av disse kanalene redoks-statusen og den elektrokjemiske balansen til cellen (179). Flere studier har funnet sammenhenger mellom nedsatt funksjon av kalsium-, kalium-, natrium- og kloridkanaler med påføring av oksidativt stress (OS) og tilknyttede patologier (175-177). Disse studiene gir ytterligere belegg for at den biofysiske mekanismen vi har presentert, er gyldig (143-146).

Kalsiumsignalering og ROS-produksjon i mitokondriene. Endring av ionekonsentrasjoner i celler vil påvirke sentrale celle-tilknyttede signaleringsveier, inkludert Ca^{2+}-signalsystemet, som regulerer en rekke celle-tilknyttede funksjoner, herunder celledeling, celledifferensiering, ROS-reguleringssystemet og apoptose (192-196). Hvis funksjonen til VGCCer i plasma eller i mitokondriers membraner hindres slik at det fører til kritiske endringer i konsentrasjoner av Ca^{2+}-ioner i celler eller i mitokondrier, slik som de endringene som skjer etter eksponering for EMF, er dette forbundet med patogenese [at det oppstår lidelser, EF] og med cytotoksisitet (195,196). Spenningsstyrte anion-kanaler i den ytre membranen av mitokondriene regulerer innstrømmingen av Ca^{2+} inn i rommet mellom membranene og i cellekjernen, og er avgjørende for ROS-produksjonen i mitokondriene. Økt nivå av Ca^{2+} stimulerer produksjon av $O_2^{\bullet}$ i elektrontransportkjeden i mitokondriene og/eller aktivering av nitrogenoksidsyntase (NOS), for å generere mer $NO^{\bullet}$. $NO^{\bullet}$ hemmer kompleks IV i elektron-transportkjeden, og utløser produksjon av enda mer ROS (109,193). ROS-overproduksjon i mitokondriene kan skade DNA både i mitokondriene og i kjernen, og sette i gang en signalkaskade som fører til celledød, noe som er funnet i menneskelige sædceller etter eksponering for EMF fra mobil-telefoni (36). Dessuten kan økte konsentrasjoner av $NO^{\bullet}$ i levende celler på grunn av aktivering av NOS forskjellige steder i cellen føre til dannelse av $ONOO^{-}$ (181,182).

Regulering av apoptose er avgjørende for å forhindre kreft (197). Imidlertid er overdreven apoptose, som påføres av økte ROS-nivåer, forbundet med inflammatoriske sykdommer og kreft (198). Når overproduksjon av ROS i en celle overbelaster kapasiteten til antioksidantsystemet i cellen, er cellen/ organismen under oksidativt stress (OS). Denne tilstanden kan føre til betydelig DNA-skade med påfølgende mangel på genomisk stabilitet og til karsinogenese (182,183,194-198).

Også K^{+}-kanaler har vist seg å være involvert i aktivering av apoptose (194), og spenningsstyrte Ca^{2+}- og K^{+}-kanaler har vist seg å være forbundet med celledeling og karsinogenese (199). Således spiller cytosoliske konsentrasjoner av Ca^{2+}- og K^{+}-ioner viktige roller i cellers funksjon og stoffskifte. I tillegg spiller spenningsstyrte kalsium- og kaliumkanaler viktige roller for at jern skal trenge inn i cellene. Jern katalyserer produksjonen av $OH^{\bullet}$ via Fenton-reaksjonen, og det kan dermed fremme toksisiteten i cellene om disse kanalenes funksjon hindres (200-202).

NADPH-oksidase og ROS produksjon. Uavhengig av den virkningen som EMF har på metalliske kationers spennings-regulerte kanaler (som Ca^{2+}, Na^{+} og K^{+}), vil også proton- (H^{+}) spenningsregulerte kanaler bli påvirket, siden de fungerer på svært likt vis (166,167). Dette vil igjen påvirke funksjonen til NADPH-oksidase, et plasmamembran-enzym som finnes i overflod i alle celler, og som normalt genererer ROS for å eliminere invaderende mikroorganismer (203,204). Aktiviteten til NADPH-oksidase er sterkt knyttet til H^{+}-kanaler, og den kan til og med virke direkte som en spenningsstyrt H^{+}-kanal på grunn av sin $gp91^{phox}$ underenhet som går gjennom membranen (205,206). NADPH-oksidase danner en elektronfluks som reduserer O_2 utenfor cellen til $O_2^{\bullet-}$ (203,207).

NADPH-oksidase aktiveres av cytosolisk Ca^{2+} og har et bindingsete for Ca^{2+} i tillegg til sin spenningsstyrte H^{+}-kanal ($gp91^{phox}$ transmembran-region) (204). Dermed vil omkalfat-ringer av konsentrasjoner internt i celler etter uregelmessig åpning/lukking av deres spenningsstyrte kanaler, påvirke funksjonen til NADPH-oksidase og utløse ROS-produksjon i utide, hva enten det gjelder H^{+} eller Ca^{2+}.

NADPH-oksidase har rimelig nok blitt foreslått som et primært mål for EMF-eksponering i levende celler. I 2007 fant Friedman *et al* (208) rask ROS-produksjon i dyrkede celler etter noen få minutters eksponering for radiofrekvente EMF som ble sendt ut fra en generator.

Na^{+}/K^{+}-ATPase og ROS-produksjon. Nedsatt funksjon av spenningsstyrte kanaler for Na^{+}, K^{+}, Mg^{2+} og Ca^{2+} kan også påvirke funksjonen til Na^{+}/K^{+}-pumpen (ATPase) og Ca^{2+}-pumpene i alle cellers plasmamembraner. Ionepumpene (som er aktive ionetransportører) tvers gjennom alle cellemembraner bestemmer membranspenningen, cellens volum og den elektro-kjemiske balansen, koordinert med ionekanalene (som er passive ionetransportører) (147,148). En forsterkningssløyfe med positiv tilbakekopling mellom Na^{+}/K^{+}-ATPase-signalering og produksjon av ROS i mitokondriene ble eksperimentelt demonstrert i primærkulturer med hjertemyocytter (209): Na^{+}/K^{+}-ATPase ble et mål for signalering som ble initiert av ROS, og stimuleringen av Na^{+}/K^{+}-ATPase-signaleringsfunk-sjonen førte i sin tur til økt ROS-produksjon. Denne modellen kan helt avgjort knyttes til dysfunksjon i levende celler som er under eksponering for EMF.

Det er derfor klart påvist at forstyrret åpning/lukking av VGICer i plasma og intracellulære membraner på grunn av EMF-eksponering mest sannsynlig vil utløse overproduksjon av ROS og derpå følgende celleskade. Selv om det alt i lang tid har vært mye data som forbinder dysfunksjon i ionekanalene med påført celledød eller kreft (194,199), har kanskje ikke koplingen til feilfunksjoner i VGICene og overproduksjon av ROS (175-179,190-192), som fører til DNA-skade, fått den oppmerksom-heten den fortjener.

I tillegg til virkningene via ROS/frie radikaler, kan også DNA-skade forårsakes av uregelrett aktivering av DNaser etter at ionekonsentrasjoner internt i celler er blitt forandret. Av de to formene for endonukleaser som er involvert i initieringen av apoptose, er en av dem Ca^{2+}-avhengig (DNase I). Økt nivå intracellulært Ca^{2+} er i noen tilfeller forbundet med økt apoptose, muligens på grunn av aktivering av DNase I (210). At DNase I kan aktiveres ved økte nivåer av intracellulær Ca^{2+}, kan dermed være en alternativ kilde til DNA-skade og tilknyttede patologier.

ROS- og DNA-skader. $OH^{\bullet}$ regnes som den oksidanten som kan ha størst virkning på DNA. Hovedmekanismen for OH-produksjon involverer den jern-katalyserte omdannelsen av H_2O_2 via Fenton-reaksjonen (211): Fe^{2+} oksideres av H_2O_2 til

Fe^{3+}, og produserer et OH^--radikal og et hydroksid-ion (OH^-) (Lign. 21). Fe^{3+} reduseres deretter tilbake til Fe^{2+} med et annet molekyl av H_2O_2, og produserer et hydroperoksylradikal og et proton (Lign. 22).

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\bullet} + OH^- \quad (21)$$

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HOO^{\bullet} + H^+ \quad (22)$$

Nettoeffekten er at to hydrogenperoksydmolekyler omdannes så det blir laget to forskjellige arter oksygenradikaler, med vann (H^++OH^-) som biprodukt.

$$2\ H_2O_2 \rightarrow OH^{\bullet} + HOO^{\bullet} + H_2O \quad (23)$$

OH^--radikalet reagerer med ethvert biologisk molekyl i sitt umiddelbare miljø, herunder DNA. For eksempel kan det bryte opp makromolekyler (R-R eller R-H) eller trekke ut atomer fra dem (så som de forskjellige hydrogenatomene i deoksyribosen) ved å bryte kovalente bindinger. Dette fører til kjemiske endringer av makromolekylene og til produksjon av nye frie radikaler ($R^{\bullet}$ eller $RO^{\bullet}$):

$$R\text{-}R + OH^{\bullet} \rightarrow ROH + R^{\bullet} \quad (24)$$

$$RH + OH^{\bullet} \rightarrow R^{\bullet} + H_2O \quad (25)$$

$$\text{eller } RH + OH^{\bullet} \rightarrow RO^{\bullet} + H_2 \quad (26)$$

De nye frie radikalene vil så reagere med andre molekyler, noe som resulterer i ytterligere kjemiske endringer. Tilsvarende belegg for DNA-skade forårsaket av $ONOO^-$ foreligger også (181).

Konklusjonen er at det foreligger en klar følgerekke av hendelser som starter med den forstyrrede og uregelrette åpningen og lukkingen av VGICene som forårsakes av EMFer og fører fram til DNA-skade og tilknyttede patologier, herunder karsinogenese.

4. Drøfting

Den foreliggende studien har gjennomgått eksperimentelle og epidemiologiske funn som forbinder eksponering for rene ELF og RF (som inneholder ELF) fra menneskeskapte EMF med DNA-skader og relaterte patologier, herunder kreft. Det er dokumentert at begge disse typene menneskeskapt EMF-eksponering kan frambringe OS (3,34,36-39,43,45,109), DNA-skade (1-55,84,85) og infertilitet (56-71). Det er også dokumentert at de samme typene EMF-eksponering er knyttet til økt kreftrisiko både hos mennesker og forsøksdyr (72-83,86-98,110-114).

Vi har forsøkt å gi en fullstendig og plausibel forklaring på biofysisk og biokjemisk grunnlag på disse funnene, som er knyttet til DNA-skader. I henhold til mekanismen som tvinger ioner til oscillering og som fører til dysfunksjon av VGICer (143-146), kan de menneskeskapte (polariserte og koherente) ELF/ULF-EMFer og de faste/variable ELF/ULF-komponentene fra modulasjon/pulsing i EMF fra moderne radiofrekvenser/trådløs kommunikasjon, endre ione-konsentrasjoner i celler ved uregelrett å åpne/lukke VGICer i cellemembranene. Dette fører til (over)produksjon av ROS som gir umiddelbar OS i cytosolen og/eller mitokondriene, og som kan skade DNA når cellene ikke klarer å gjenopprette elektrokjemisk balanse (normale ioniske konsentrasjoner i cellen). Som følge kan det oppstå DNA-skader som fører til svekket reproduksjonsevne, til nevrodegenerative sykdommer, aldring, genetisk skadelige endringer og kreft.

I følge den framlagte biofysiske mekanismen er den biologiske aktiviteten til et polarisert/koherent EMF proporsjonal med dens intensitet, omvendt proporsjonal med dens frekvens, og den dobles for pulserende felt, noe som betyr at ELF/ULF EMFene og i enda større grad de pulsede radiofrekvente EMFene med ELF-pulseringer, slike som f.eks. alle EMFer fra trådløs kommunikasjon, kan forutsies å være de mest bioaktive. Dette forklarer både de virkningene som er registrert fra rene ELF EMFer (1-5,9,13-18,22,47, 50,72-82,117,212) og virkningene fra modulerte/fast eller variabelt pulserende radiofrekvente elektromagnetiske felt (RF-EMF) (1,3,4,6-8,19-21,23-46,48,49,51-55,57-71,84-107,109-114,118, 121-126). Som understreket over, benytter alle typer RF-eksponering fra alle typer antenner og enheter for trådløs kommunikasjon (TK-EMF), nødvendigvis kombinasjoner av radiofrekvente bærebølger og ELF/ULF-komponenter i form av fast pulsering, modulasjon og tilfeldige variasjoner. Det radiofrekvente bæresignalet alene inneholder ikke informasjon. Det er alltid i ELF-signalene, som modulerer det radiofrekvente bæresignalet, at informasjonen ligger (4). Betydelige eksperimentelle belegg viser at de biologisk aktive parameterne i et slikt komplekst signal er dets ELF-komponenter, og at ikke-modulerte og ikke-pulserende RF-signaler alene vanligvis ikke utløser biologiske virkninger (4,44,45,151-159), bortsett fra når de har høy nok frekvens og intensitet til å føre til oppvarming (128,168-170). Derfor fremsetter den foreliggende studien den antakelse at det store flertallet av ikke-termiske virkninger som til nå er tilskrevet ulike typer radiofrekvente EMF-eksponeringer, rent faktisk skyldes deres ELF/ULF-komponenter.

Den biofysiske mekanismen vi har redegjort for og regneeksemplene vi har gitt, viser at det er de direkte ELF elektriske feltene (og de magnetisk induserte elektriske feltene ved plutselige pulser) som er de biologisk aktive komponentene, ikke de magnetiske feltene, i motsetning til det som før har vært vurderingen til helseaktører og -myndigheter (117), og dette er i samsvar med tidligere eksperimentelle funn (191): Elektriske felt trenger riktignok dårligere gjennom levende vev enn magnetfelt da deres gjennomtrengningsevne avhenger av den omvendte kvadratroten av frekvensen. Men ELF elektriske felt har likefullt betydelig gjennomtrengningsevne, ettersom gjennomtrengningsevnen også avhenger av den omvendte kvadratroten av mediets ledningsevne (213). Riktignok er sjøvann mye mer ledende enn levende vev, men ELF-elektromagnetiske bølger (altså både de elektriske og magnetiske delene av bølgene) trenger mange meter ned i sjøvannet og muliggjør kommunikasjon med ubåter (214). Dessuten er det kjent at isolert vev reagerer både på eksternt påførte pulserende og sinusformede elektriske ELF-felt og har svært lave terskler (~10^{-3} V/m), og som ligger i nærheten av de terskler som den framlagte teorien forutsier (143,215-217). Dette belegget viser at elektriske ELF-felt trenger tilstrekkelig inn i levende vev til å påføre vevet virkninger, selv ved svært lave feltintensiteter. Og til slutt kan nevnes at hudceller, nervenes endepunkter, øyne og slike organer nær overflaten som hjernen og hjertet blir direkte utsatt for eksternt påførte elektromagnetiske felt. Av disse grunnene skilles det ikke mellom ELF-elektriske felt som kommer innenfra eller tilføres utenfra.

Mekanismen/teorien om ione-påtvungen oscillering er beskrevet i den foreliggende studien ved hjelp av realistiske ligninger basert på de kreftene som utøves av eksternt påførte

menneskeskapte (polariserte) EMF på frie ioner i nærheten av spenningssensorene til VGICer i cellemembraner. Ved å løse den grunnleggende Lign. 2, kom vi fram til betingelser for biologisk aktivitet der intensiteten til et påført polarisert EMF ses i sammenheng med dets frekvens. Fra Betingelsene 8-10 og 16-18 for biologisk aktivitet kunne vi så utlede de biologisk aktive kombinasjonene av intensiteter og frekvenser fra kontinuerlige og pulserende elektriske og magnetiske felt som vi har angitt over. Tallene som kom ut av dette, forklarer nesten alle eksperimentelle og epidemiologiske funn som knytter biologiske/helseeffekter med eksponering for menneskeskapt EMF.

Denne mekanismen ble første gang publisert i 2000 (144) og var da basert på de den gang tilgjengelige data om strukturen og funksjonen til VGICene. Likefullt har nyere detaljer om rollene til S1-S6-helikser, kanalstruktur, avspenning, hysterese og åpning/lukking ikke tilbakevist, men bekreftet og utvidet denne forståelsen (162,163,165,218-221).

Det som er vanskeligere å forklare, er eksistensen av ikke-lineære fenomener som 'vinduer' med økt biologisk aktivitet som er rapportert nå og da i litteraturen om biologiske virkninger fra EMF, der visse virkninger forsterkes innenfor visse verdier av en parameter for EMF-eksponering (som oftest intensitet eller frekvens) (1,40,151–153,222). At det fins 'vinduer' viser at levende cellers/organismers respons på EMF ikke er helt proporsjonal med de nevnte parameterne for EMF. Ikke-lineære responser fra levende celler er ikke blitt grundig utforsket, og det vil ta flere år før de er det. Sett opp mot den mekanismen som er beskrevet her, er det blitt foreslått som en mulig forklaring på observerte 'intensitetsvinduer' at de skyldes at det kan finnes en øvre grense for den spenningsendringen som vil føre til åpning/lukking av membranen (222). En slik øvre grense ser ut til å finnes. VGICene reagerer på spenningsendringer i membranen fra ~30 mV (minimum) til ~100 mV (maksimum), der kanalens ledningsevne mettes (218,221). Utover denne mulige forklaringen er det så langt ikke gitt noen annen forklaring på de observerte 'vinduseffektene'.

En virkning som ikke omfattes av Lign. 11 og 12 for den biologiske aktiviteten, er den sterkere biologiske påvirkningen [som observeres] fra sterkt varierende, og fra uforutsigbart varierende, eksponering, slik som eksponeringen fra trådløst kommuniserende enheter (herunder mobiltelefoner og WiFi) og fra tilsvarende senderanlegg (4,121,122). Den beskrevne mekanismen leder til presise forutsigelser når de anvendte EMFene har konstante parametere (intensitet og frekvens, blant annet). Men når parameterne er svært variable, og uforutsigbart variable, kan denne mekanismen, og enhver annen mulig mekanisme, bare gi anslag for virkninger utfra gjennomsnitts- og maksimalverdier for eksponeringen fra de ulike EMFene. Og endelig omfatter ligningene for biologiske virkninger bare parametere for felt (og vev), og ikke slike eksponeringsvariabler som eksponeringens varighet eller pulsingens hyppighet, som også er svært viktige (16,17,19,41,55,122). En måte å ta med slike parametere på, er å multiplisere de riktige delene av Lign. 11 og 12 med bestemt(e) koeffisient(er), som eventuelt må anslås eksperimentelt. Dette kan være et tema for fremtidig utvikling av teorien.

Denne teorien har for første gang lykkes i å forklare at dyr kan sanse kommende jordskjelv, og den sansingen som følsomme enkeltpersoner har av kommende tordenvær, og den har gjort det gjennom virkningen av de delvis polariserte naturlige EMFene som er forbundet med disse fenomenene (146,223).

Enhver 'mekanisme' i vitenskap (spesielt i fysikk) må være basert på enkle og rimelige postulater, og må nødvendigvis uttrykkes kvantitativt (ved hjelp av løsbare ligninger og tall). Verdiene til de ulike parameterne i ligningene må baseres på fysiske/molekylære data. Kvalitative beskrivelser alene, eller ufullstendige kvantitative beskrivelser basert på ufullstendige eller uløselige ligninger, utgjør ikke en 'mekanisme'. Den framlagte biofysiske mekanismen (143-146) er den eneste som oppfyller de nevnte kriteriene når det gjelder biologiske virkninger påført av EMF. Tidligere viktige forsøk på å identifisere mekanismer har fokusert på ioner som beveger seg inne i membrankanaler eller i andre proteiner (224-227), men har ikke vært vellykkede, hovedsakelig av følgende årsaker: i) De tok ikke hensyn til dempnings- og gjenoppbyggingskrefter (224,226), eller de beregnet dem ikke (225,227). Det vanskelige var ikke å ta slike krefter med i vurderingen, da dette er standard i oscilleringsmekanikk, men å beregne deres parametere, slike som β og ω_o, og den maksimale hastigheten til ionet (u_o) inne i en kanal. ii) De vurderte ikke den samordnede bevegelsen av flere ioner som svinger parallelt og i fase på grunn av polarisering og koherens, og dermed utøver additive krefter på kanalsensorer som overgår de større, men kaotiske, kreftene fra ionenes tilfeldige termiske bevegelser. iii) De satte søkelyset på magnetiske felt og magnetisk påførte elektriske felt, og ignorerte eksternt påførte elektriske felt, som faktisk ser ut til å være mer biologisk aktive (191). iv) De kom ikke fram til tall for hvilke feltintensiteter som ved hvilke frekvenser er nødvendige for å påvirke celler, selv om riktignok noen eksperimentelle rapporter har pekt på bioaktive frekvenser nær de som forutsies av Liboffs ion-syklotron-resonans- (ICR) modell (224,228). Dette kan tyde på at det fins en ytterligere/sekundær resonansmekanisme som har å gjøre med ICR-fenomener (169). v) Bortsett fra studien av Balcavage *et al* (226), har fokuset ganske enkelt vært rettet mot ioners bevegelser i kanaler/proteiner, og ikke mot åpning/ lukking av VGICer, som jo er langt mer sannsynlig som mekanisme for å sette i gang biologiske virkninger.

Også flere andre forslag til mulige mekanismer støter på problemer som er knyttet til grunnleggende spørsmål (229-231). Det som Pall betegner som en 'VGCC-aktiveringsmekanisme' og har presentert som hans egen oppdagelse, er ganske enkelt den mekanismen som vi har lagt fram her. En kommentar-artikkel/brev til redaktøren er blitt publisert om de betydelige etiske sidene ved dette (129). En utvidet gjennomgang av foreslåtte mekanismer er skrevet av Creasey og Goldberg (169).

Det er blitt hevdet at ELF-komponentene til de komplekse RF-ELF EMFer som trådløs kommunikasjon består av, må 'demoduleres' for å kunne sanses av levende organismer (232). 'Demodulert' eller ikke, faktum er at ELF-komponentene til modulerte/pulsede signaler brukt i trådløs kommunikasjon kan merkes direkte av både ELF-målere/spektrumanalysatorer og av levende organismer (40,55).

Selv om det siden 2000 er publisert en rekke oppfølgere om denne mekanismen (144), er emnet fortsatt av stor betydning, og i hver påfølgende publikasjon er ytterligere viktige sider blitt belyst og/eller rendyrket. I vår tidligere studie fra 2002 (145) ble mekanismen utvidet til å omfatte oscillerende magnetiske felt og det termiske støyproblemet ble diskutert mer inngående, mens i 2015 (143) ble mekanismen brukt til å avdekke den store betydningen som polarisering/koherens har for den biologiske påvirkningen fra menneskeskapte elektromagnetiske felt. I 2017 (223) og 2020 (146) ble så dette brukt til å forklare sensitive menneskers/dyrs sansning av kommende tordenvær og kommende jordskjelv. I den foreliggende studien er flere aspekter raffinert ytterligere, herunder: i) avstanden til S4-sensorer fra kanalporen; ii) flere detaljer om dempnings-koeffisienten β og bioaktivitetskonstanten k (Lign. 11); iii) ytterligere forklaring av rollen til konstantleddet i løsningen

(Lign. 3); iv) likheten mellom proton-spenningsstyrte kanaler og de andre VGICene; v) numeriske eksempler som viser den evnen som de pulserende ELF elektriske og magnetiske feltene i 2G/3G/4G mobiltelefoni, DECT, WiFi, Bluetooth og ELF-feltene fra kraftlinjer har til å påføre biologiske/helsevirkninger; vi) hastigheten til oscillerende ioner; vii) utvidelse av diagrammet over biologisk påvirkning til intensiteter ned til 10^{-5} V/m; og viii) drøfting av andre foreslåtte mekanismer.

Videre har den foreliggende studien dokumentert hvordan hindringer i funksjonen til VGICer på membranene til levende celler utløser (over)produksjon av frie radikaler/ROS, slik som den særdeles potente $OH^{\bullet}$ som blir dannet av H_2O_2 via Fenton-reaksjonen, og $ONOO^-$ som blir dannet av $NEI^{\bullet}$. Disse regnes som de viktigste av de artene som er skadelige for DNA og andre kritiske biologiske molekyler. Det er anslått at omtrent to tredjedeler av DNA-skaden som forårsakes av ioniserende stråling, skyldes $OH^{\bullet}$ (233,234). Mens $OH^{\bullet}$ bare kan spre seg over avstander som kan sammenlignes med lengden til et makromolekyl, kan H_2O_2 bevege seg til et hvilket som helst sted i cellen. Selv om den høye reaktiviteten til det særdeles potente $OH^{\bullet}$ gjør at det har en ekstremt kort levetid (i størrelsesorden 10^{-9} - 10^{-4} sekunder, avhengig av hvilke andre molekyler som er tilstede), kan det dannes av H_2O_2 på ethvert sted i cellen (herunder i kjernen) og virker øyeblikkelig på DNA og andre makromolekyler (233,234). Når det gjelder $NO^{\bullet}/ONOO^-$ kan de spre seg til hvor som helst i cellen og dermed direkte påvirke ethvert molekyl, herunder DNA (181). Selv om den foreliggende studien har identifisert spesifikke veier fram mot overproduksjon av ROS og frigjøring av DNaser som er forbundet med forstyrrede ione-konsentrasjoner i EMF-eksponerte celler, trenger de eksakte molekylære mekanismene å utforskes og belyses ytterligere.

Til slutt har denne studien diskutert hvordan ureparerte/feilreparerte DNA-lesjoner/skader, så som trådbrudd, kovalente bindingsbrudd eller nukleotidbaseskader, fører til cellealdring, celledød og/eller mutasjoner, og til relaterte patologier, herunder kreft. Selv om det har utviklet seg effektive mekanismer i alle dyr/celler for å reparere DNA-skader som påføres av miljøstressorer, er det stor forskjell på følgene når de skadelige hendelsene er isolerte eller tilfeldige (f.eks. radioaktive partikler eller γ-fotoner fra kosmisk/naturlig radioaktivitet, eller eksponering for sporadisk røntgenstrålediagnostikk), sammenlignet med vedvarende/gjentatt eksponering for virkestoffer som er giftige for celler, selv når disse midlene er forholdsvis svakere. Eksponering for menneskeskapte elektromagnetiske felt, og spesielt for de mest skadelige fra antenner/-enheter for trådløs kommunikasjon og høyspentlinjer (4), er blitt en ny realitet i det moderne liv. Milliarder av mennesker utsettes daglig for slike EMF. Selv om de er mindre cytotoksiske enn radioaktivitet og visse cytotoksiske kjemikalier, utgjør disse de cellegiftige stressorene som er mest vedvarende tilstede i det daglige, og som ingen reparasjonsmekanismer kan motvirke tilstrekkelig effektivt. De cytotoksiske stoffene som vi omgås fra før, eksponerer oss derimot tilfeldig som isolerte hendelser. Når en organisme konstant er under oksidativt stress (OS) på grunn av et helt nytt cytotoksisk stoff som menneskeskapte EMF, kan ingen beskyttelsesmekanisme som har utviklet seg i løpet av milliarder av år med biologisk evolusjon for å beskytte mot naturlige (ikke-polariserte) EMF/stråling eller mot isolerte helsefarlige hendelser, være tilstrekkelig effektiv.

Cellenes evne til reparasjon som respons på DNA-skade er avgjørende for det endelige utfallet. Skadeterskelen som må overskrides for at skaden blir uopprettelig, avhenger av celletypen og av organismens helse og tilstand. En organisme med dårlig helse og/eller under stress og betennelse på grunn av OS kan forventes å ha redusert reparasjonsevne og økt kreftrisiko. Også epigenetiske virkninger, så som endret genuttrykk, kan føre til at cellers funksjonsevne ødelegges og til karsinogenese (133,235,236).

Både DNA-skade og skadelige endringer i proteinsyntesen, særlig økte nivåer av stressproteiner, er rapportert frambrakt på samme måte både av ELF og av pulserende RF-EMF (237,238). Virkningene av pulserende radiofrekvenser ble imidlertid tilskrevet bærefrekvensen, og det ble ikke vurdert at ELF-komponentene kanskje i begge tilfeller (ELF og pulserende RF) kunne være ansvarlige for virkningene, slik det nå foreslås av den framlagte studien.

Så vidt vi kjenner til, gir denne studien for første gang et fullstendig og presist biofysisk/biokjemisk bilde som kan forklare det store antallet eksperimentelle og epidemiologiske funn som forbinder menneskeskapt EMF-eksponering med DNA-skade og tilhørende patologier som kreft, infertilitet og nevrodegenerative sykdommer.

De eksperimentelle og epidemiologiske funnene som forbinder eksponering for menneskeskapte EMFer og DNA-skader, infertilitet og kreft, har nå eksistert lenge. Nå er de forklart av den fullstendige mekanismen som er lagt fram her. Den foreliggende studien bør danne grunnlag for videre forskning og oppmuntre helsemyndigheter til å iverksette tiltak for å beskytte liv på Jorden mot ubegrenset bruk av menneskeskapte EMF.

Takk til
Ikke aktuelt.

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Forfatternes bidrag
DJP designet studien og skrev hovedmanuskriptet. AK verifiserte alle ligninger og beregninger. IY var medforfatter av avsnitt 3 om biokjemiske prosesser. GPC gjennomgikk og evaluerte alle data. Alle forfattere har lest og godkjent manuskriptet. Dataautentisering er ikke aktuelt.

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Forfatterne erklærer at de ikke har noen konkurrerende interesser.

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Human-made electromagnetic fields: Ion forced-oscillation and voltage-gated ion channel dysfunction, oxidative stress and DNA damage (Review)

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Abstract. Exposure of animals/biological samples to human-made electromagnetic fields (EMFs), especially in the extremely low frequency (ELF) band, and the microwave/radio frequency (RF) band which is always combined with ELF, may lead to DNA damage. DNA damage is connected with cell death, infertility and other pathologies, including cancer. ELF exposure from high-voltage power lines and complex RF exposure from wireless communication antennas/devices are linked to increased cancer risk. Almost all human-made RF EMFs include ELF components in the form of modulation, pulsing and random variability. Thus, in addition to polarization and coherence, the existence of ELFs is a common feature of almost all human-made EMFs. The present study reviews the DNA damage and related effects induced by human-made EMFs. The ion forced-oscillation mechanism for irregular gating of voltage-gated ion channels on cell membranes by polarized/coherent EMFs is extensively described. Dysfunction of ion channels disrupts intracellular ionic concentrations, which determine the cell's electrochemical balance and homeostasis. The present study shows how this can result in DNA damage through reactive oxygen species/free radical overproduction. Thus, a complete picture is provided of how human-made EMF exposure may indeed lead to DNA damage and related pathologies, including cancer. Moreover, it is suggested that the non-thermal biological effects attributed to RF EMFs are actually due to their ELF components.

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Abbreviations: DECT, digitally enhanced cordless telecommunications; ELF, extremely low frequency; EMF, electromagnetic field; MT, mobile telephony; OS, oxidative stress; RF, radio frequency; ROS, reactive oxygen species; ULF, ultra low frequency; VGICs, voltage-gated ion channels; VGCCs, voltage-gated calcium channels; WC, wireless communications; Wi-Fi, wireless fidelity; 2G/3G/4G/5G, second/third/fourth/fifth-generation of mobile telephony

Key words: EMF, ion forced-oscillation, VGICs, free radicals, OS, ROS, DNA damage, cancer

Contents

1. Introduction

Experimental and epidemiological findings connecting exposure of living organisms to ELF and complex RF human-made EMFs with genetic damage, infertility and cancer. There is a plethora of experimental findings connecting the *in vivo* or *in vitro* exposure of experimental animals or cells to extremely low frequency (ELF) (3-3000 Hz) or radio-frequency (RF)/microwave (300 kHz-300 GHz) electromagnetic fields (EMFs), with genetic damage/alterations

(DNA damage, chromosome damage and mutations, among others), cell death and related effects (1-4). Most findings concern exposure to wireless communication (WC) EMFs [from mobile phones/antennas, cordless domestic phones (DECT: digitally enhanced cordless telecommunications), internet (Wi-Fi: wireless fidelity) or 'Bluetooth' wireless connections, among others], which necessarily combine RF/microwave carrier frequencies with ELF pulsing and modulation, and ultra low frequency (ULF) (0-3 Hz) random variability of the signal. Today, almost all technical RF EMFs (not only of WC, but also from radars, radio and television antennas, among others) contain ELF/ULF components in the form of on/off pulsations, modulation, and signal variability. These are usually called simply 'RF', but actually they are a combination of RF and ELF/ULF (4).

The number of experimental-laboratory studies showing genetic damage and related effects induced by human-made ELF or RF (combined with ELF) EMFs on a variety of organisms/cell types under different experimental conditions has rapidly increased, especially in recent years (5-55).

Several of the aforementioned findings involve DNA damage and consequent cell death in reproductive cells of different animals, resulting in decreased reproduction. In particular, the effects of pulsing WC EMFs on the DNA of reproductive cells, as reported by different studies on a variety of animals (25,30,31,36,40,41,46), display a marked similarity and explain other findings that connect WC EMF exposure with insect, bird and mammalian (including human) infertility (56-64), or declines in bird and insect populations (especially bees) during the past 15 years (65-69). A significant decrease in reproduction (decrease in egg laying or embryonic death) after exposure to mobile telephony (MT) radiation was identically observed in fruit flies (30,40,57,58), chicken eggs (61), birds (65-67), and bees (63). Similar effects are reported for amphibians (70,71), rats (31,62), and human sperm (decreased number and motility of spermatozoa) (59,60). These markedly similar findings in different organisms by different research groups can be explained by the observed cell death in reproductive cells after DNA damage, as seen in fruit fly ovarian cells (30,40,41,46), human sperm cells (36), mouse and rat sperm cells (25,31). Decreased reproduction after DNA damage and cell death in reproductive cells or embryonic death induced by purely ELF EMF-exposure is also reported (4,9,14,22,47).

At the same time, epidemiological/statistical studies increasingly link man-made EMF exposure with health problems, genetic damage and cancer in human populations. More specifically, ELF EMFs from power lines and high-voltage transformers (mainly 50-60 Hz plus additional frequencies due to harmonics, noise and discharges, among others) are linked with childhood leukemia (72-82) for magnetic field intensities down to 2 mG (0.2 μT) (76,82), or distances from power lines up to 600 m (81), and electric field intensities down to 10 V/m (78). RF exposure from various antennas always containing ELF components, especially MT antennas, is linked to various forms of cancer. Hallberg and Johansson (83) found a connection between skin cancer (melanoma) incidence in humans and residential exposure to radio broadcasting antennas, while two recent studies found significantly increased genetic damage in the peripheral blood lymphocytes of people residing in the vicinity of MT base antennas (84,85). During the past 15 years, epidemiological studies have found an increasing association between mobile or cordless phone use and brain tumors in humans (86-98). Moreover, during the past 20 years, statistical studies have found associations between exposure to MT base station antennas and devices, and reported symptoms of un-wellness referred to as 'microwave syndrome' or 'electro-hypersensitivity' (EHS). The symptoms include headaches, fatigue, sleep disorders, etc. (99-107). A high percentage (~80%) of EHS self-reporting patients were recently found with increased oxidative stress (OS) [intracellular increase in free radicals/reactive oxygen species (ROS)] in their peripheral blood (108).

A review of studies involving exposure to complex RF EMFs with ELF pulsation/modulation revealed that 93% of them reported induction of OS/ROS overproduction in biological systems (109).

Induction of cancer in experimental animals by long-term MT exposure, including ELF pulsations, has also been reported (110,111). A recent study of the USA National Toxicology Program (NTP) found that rats exposed for 2 years, 9 h per day, in the near-field of simulated 2nd generation (2G) or 3rd generation (3G) MT emissions, developed brain cancer (glioma) and heart cancer (malignant schwannoma), with both lower and higher radiation levels than the officially accepted limits (112). Moreover the study found significantly increased DNA damage (strand breaks) in the brains of exposed animals (113), confirming that DNA damage is closely related to carcinogenesis. An Italian life-span exposure study of rats in a simulated 2G MT far-field also found induction of heart schwannomas and brain glial tumors, confirming the results of the NTP study (114).

These findings on animal carcinogenicity along with the epidemiological cancer findings on humans, the DNA damage and OS findings, and the adverse effects on reproduction due to DNA damage in the gametes or embryonic death, point towards the same direction, i.e., that human-made EMF exposure causes OS and DNA damage that may lead to cancer, reproductive declines and related diseases. It is important to note that the exposure levels in the vast majority of all the aforementioned studies (1-114) were significantly below the officially accepted exposure limits for ELF and RF EMFs, which have been set to prevent discharges on humans in the case of ELF and heating of living tissues in the case of RF (115,116).

At the same time, several other studies have reported no effects of ELF or RF EMFs in all the aforementioned end-points (1-4,47,57,115-124), especially studies that employed simulated MT/WC exposure from generators with invariable parameters (intensity, frequency and pulsations, among others) and no modulation or random variability. By contrast, more than 95% of the studies that employed real-life MT/WC exposure from commercially available devices (mobile/cordless phones and Wi-Fi, among others) with high signal variability found effects (4,121,122). Regardless of real-life or simulated exposure, the majority of experimental studies (more than 70%) both in the RF (combined with ELF) and purely ELF bands do find effects (4,109,123,124). In a recent review of 138 RF studies with frequencies >6 GHz evaluating potential effects of the under deployment 5th generation (5G) MT/WC system, it was not specifically examined whether there were

ELF components in the exposure and what type, or whether there was any similarity between the signals produced by generators in the studies, and those of the 5G, apart from the carrier frequency. While most of the reviewed studies reported effects, they were criticised in this review for not being 'independently replicated' and for employing 'low quality methods of exposure assessment and control' (125). Thus, despite the incomplete review methodology, the authors of the review attempted to downgrade any reported effects.

Under the increasing weight of scientific evidence, the International Agency for Research on Cancer (IARC) has for a long time now classified both ELF and RF EMFs as possibly carcinogenic to humans (group 2B) (117-119). Based on additional scientific evidence after the 2011 IARC classification for RF EMFs, several studies have suggested that RF/WC EMFs should be re-evaluated and classified as probably carcinogenic (group 2A) or carcinogenic (group 1) to humans (92,97,126,127). As already emphasized, in the vast majority of studies characterized as 'RF', the ELF/ULF components were present.

While the reported effects in the vast majority of the above studies (1-124) induced by ELF or complex RF (containing ELF) EMFs were not accompanied by any significant heating of the exposed living tissues, it is well established that purely RF/microwave EMFs cause heating of exposed materials (e.g. microwave ovens). The heating becomes significant for high power/intensity (≥0.1 mW/cm^2) and high frequency (at GHz range) microwaves (128). In addition, purely RF EMFs, which are of very limited technological use, are scarcely reported to induce non-thermal effects, and it is questionable in such cases, whether the presence of any ELFs was carefully excluded (129).

DNA damage and related pathologies. It is well documented that DNA damage is connected with cell senescence (cell aging and loss of replicative capacity), cell death, neurodegenerative diseases and aging of an organism, and is the main cause of carcinogenesis induced by environmental stressors (3,130-138). DNA damaging events take place at any time in the cells of any living organism due to a variety of events (such as exposure to ultraviolet radiation, natural radioactivity or cytotoxic chemicals), but efficient DNA repair mechanisms have evolved to provide protection. Damage in the DNA is any modification in a nucleotide base, deoxyribose, a break in a covalent bond between deoxyribose and nucleotide base, or a break in a phosphodiester bond in one or both strands (3,130-139).

Replication of damaged (or inaccurately repaired) DNA that may occur before repair or blocking can lead to gene mutations, which will then give rise to altered proteins. Mutations in oncogenes, tumor-suppressor genes, DNA repair genes or genes that control the cell cycle can generate a clonal cell population with a distinct ability to proliferate. DNA methylation that may prohibit the expression of DNA repair genes and synthesis of related proteins can result in inaccurate ('error-prone') DNA repair. Many such events, which may accumulate over a long period of time in cases of chronic exposure to carcinogens, can lead to genomic instability and cancer (133,134,136,139).

When the genomic DNA of a cell is damaged by an external stressor and the damage is either not reparable or inaccurately repaired, the following outcomes are possible: i) The cell dies (necrosis) or is led to suicide (induced apoptosis). In the case of cell types with the ability to proliferate, the organism compensates for their loss by creating new cells, practically with no adverse consequences apart from energy consumption, which may lead to accelerated aging when such events occur at a high rate. In the case of cell types that do not have ability to proliferate, such as neural cells or chondrocytes, the loss of a significant number of cells will probably result in the inability of certain tissues/organs to operate normally. In the case of neural cells, this may lead to neurodegenerative diseases such as Alzheimer and Parkinson, and autoimmune disorders, among others. ii) The cell does not die but survives with modified DNA. In the case of somatic cells that proliferate, the modified genome will reproduce itself. Even though the organism may recognize such mutant cells as foreign and try to isolate them and remove them, they strive to survive and may start proliferating uncontrollably, initiating cancer. In the case of reproductive cells (oocytes and spermatocytes), this may lead to mutated new organisms that may be problematic in many ways or cancer-prone. In both cases (somatic or reproductive cells) cell senescence is an alternative pathway for eliminating surviving genetically defective cells. Thus, cells with irreparably damaged genomic DNA will result in cell senescence, cell death, cancer or mutated offspring, depending on cell type and specific biological/environmental conditions (3,4,122,130-132,135-137).

The duration of cancer development (latency period) after irreparable DNA damage may be a number of years, depending on the organism and the type of cancer. The latency period for gliomas (a type of brain cancer) is usually >20 years in humans (140). This probably explains why only during the past ~15 years epidemiological studies have started showing an association between mobile phone use and cancer (86), whereas cancer from power lines, which are several decades older than MT/WC, has been indicated long before (72).

Purpose of the present study. As aforementioned, a growing number of experimental and epidemiological/statistical findings connect man-made EMF exposure with genetic damage and cancer, and this involves the breakage of chemical/electronic bonds in molecules/atoms, in other words ionization. The human-made EMFs with frequencies up to the lower limit of infrared (0-3×10^{11} Hz) discussed in the present study cannot directly cause ionization, except for very strong field intensities (≥10^6 V/m) (141,142). Such field intensities rarely exist environmentally, apart from atmospheric discharges (lightning) or in very close proximity to high-voltage power lines and transformers. The question therefore is how human-made EMFs at environmental intensities are capable of damaging DNA and other biological molecules. Obviously they have the ability of breaking chemical bonds indirectly through the action of some primary biophysical mechanism(s) and subsequent initiation of intracellular biochemical processes.

Visible and infrared natural light cannot break chemical bonds, even though they expose us at higher frequencies and radiation intensities than human-made EMFs in daily life (143). There must be a unique property of the human-made EMFs that makes them capable of inducing

adverse biological/health effects and ionization, in contrast to natural infrared and visible light. This unique property is that human-made EMFs/radiation are totally polarized and coherent, meaning that they possess net electric and magnetic fields, apart from radiation intensity, which exert forces on any electrically charged (or polar) particle/molecule such as mobile/dissolved ions and charged macromolecules in any biological system (143).

The purpose of the present study is to suggest a realistic primary biophysical mechanism for polarized and coherent EMFs at environmentally relevant intensities, to impair cellular function and initiate plausible intracellular biochemical processes resulting in genetic damage and carcinogenesis, as reported in the aforementioned studies.

2. Biophysical action of polarized/coherent EMFs resulting in voltage-gated ion channel (VGIC) dysfunction and disruption of cell electrochemical balance

It has been shown that polarized/coherent EMFs, even at very low field intensities in the ULF and ELF bands, can cause irregular gating of electro-sensitive ion channels or VGICs on the cell membranes through the 'ion forced-oscillation mechanism' (143-146), with consequent disruption of the cell's electrochemical balance (the electrical and osmotic equilibrium maintained by specific concentrations of all dissolved/mobile ions across all cell membranes according to the Nernst equation) (144,147,148). Since, as explained, ELF/ULF components exist also in the complex WC/RF EMFs, this mechanism, which will be thoroughly reviewed next, accounts for the biological effects of the vast majority of human-made (polarized and coherent) EMFs.

The mechanism is based on molecular/physical data, and the forces on mobile ions, in the vicinity of the voltage-sensors of VGICs, exerted by an applied polarized oscillating EMF. The oscillating field will force mobile ions to oscillate on parallel planes and in phase with the field. This coordinated motion of electrically charged particles exerts electric forces on the voltage-sensors, similar to the forces exerted on them by changes in the transmembrane electric field known to physiologically gate these channels, and thus the channels are gated irregularly by the applied EMF. The forces are proportional to the amplitude of the forced-oscillation, and thus, the amplitude is a direct measure of the bioactivity of the applied EMF. It has been shown that the amplitude (bioactivity) is proportional to EMF intensity, inversely proportional to EMF frequency and doubles for pulsed EMFs. The validity of the proposed mechanism has been verified by numerical testing, while other previously suggested mechanisms have failed to pass the same test (149,150). Repeated irregular gating of electro-sensitive ion channels disrupts cellular electrochemical balance and homeostasis (147,148), leading to overproduction of ROS/free radicals as described next.

It is known from a plethora of experimental data that the most bioactive EMFs are the lower frequency ones (ELF/ULF). In numerous cases of induced biological effects by complex RF EMFs modulated by ELFs, it has been found that the modulation (ELF) and not the carrier (RF) is responsible for the recorded effects. In addition, it has been repeatedly found that pulsing RF EMFs with ELF pulse-repetition rates are more active biologically than continuous (non-pulsed) fields of identical other parameters (1-5,44,45,47,151-159). These findings are in direct agreement with the described mechanism.

Biological molecules of critical importance such as ions, water molecules, proteins, nucleic acids and lipids, among others, are either polar or carry a net electric charge (147,148). The net electric field from an infinite number of individual electric pulses of random polarization and/or random phase (as e.g. photons of natural light) tends to zero at any moment (and similarly the net magnetic field).

$$\lim_{n\to\infty}\sum_{i=1}^{n}\vec{E}_i = \quad \vec{E}_1+\vec{E}_2+\vec{E}_3+\ldots+\vec{E}_n = 0 \qquad (1)$$

Thus, non-polarised/incoherent EMFs (as e.g. light and cosmic microwaves) at any radiation intensity cannot cause any parallel/coherent oscillation of charged/polar molecules (143). On the contrary, polarized and coherent (human-made) oscillating EMFs force all charged/polar molecules in biological tissue to oscillate on planes parallel to their polarization and in phase with them. This is crucially important for understanding the mechanism described. The forced-oscillation will be most intense on the mobile ions, the smallest charged particles dissolved in large concentrations in the cytosolic and extracellular aqueous solutions in all living cells/tissues controlling practically all cellular/biological functions (147,148).

Even though all molecules move randomly with much greater velocities/displacements due to thermal energy, this has no biological effect other than increasing tissue temperature. By contrast, a polarized and coherent oscillation of much lower energy than average thermal molecular energy can initiate biological effects (143-145).

The majority of cation channels (Ca^{2+}, K^+, Na^+ and H^+, among others) on the membranes of all animal cells are voltage-gated (147,148). These ion channels convert between open and closed states when the electrostatic force on their voltage sensors, due to transmembrane voltage changes, exceeds some critical value. The voltage sensors are four symmetrically arranged, transmembrane, positively charged α-helices, each one named S4. The S4 helices occupy the 4th position in a group of 6 parallel α-helices (S1-S6). The channel consists of four identical such groups in symmetrical positions around the pore of the channel. The S5-S6 helices of the four groups form the pore walls (147,148). More specifically, the sensors are positive Lys and Arg amino acids in the S4 helices. Changes in the transmembrane voltage of the order of ~30 mV are normally required to gate electrosensitive channels (change their status from opened to closed and vice-versa) (160,161). Among the S1-S4 α-helices, the S4 helices are the closest to the pore-forming S5-S6 helices, being <1 nm in distance from the pore (162,163). Several ions may interact simultaneously at any instant with an S4 sensor from a distance of the order of 1 nm, as, except for the ion(s) that may be passing through the pore any moment or are just outside the gate ready to pass, a few more ions are bound close to the pore at specific ion-binding sites (e.g. three in potassium channels) (164,165). Proton voltage-gated channels studied more recently also contain S4 transmembrane helices with charged Arg residues as voltage-sensors, similar to the metallic cation channels (166,167).

Let us consider four identical mobile ions at distances of the order of 1 nm from the channel-sensors (S4) and an externally applied oscillating EMF. The average electric (and magnetic) force on each ion due to any non-polarized EMF is zero (Eq. 1). By contrast, the force due to a polarized field with an electrical component E, is $F=Ezq_e$, (with zq_e the electric charge of the ion).

In the most usual and simplest case of a sinusoidal alternating electric field, $E=E_o\ sin\omega t$, the motion (forced-oscillation) equation of a mobile ion is as follows (143-146):

$$m_i \frac{d^2r}{dt^2} + \beta \frac{dr}{dt} + m_i\, \omega_o^2\, r = E_o\, z\, q_e\ sin\omega t \tag{2}$$

where m_i is the mass of the ion, r is the displacement of the ion due to the forced-oscillation, z is the valence of the ion (z=1 for K^+, Na^+ or z=2 for Ca^{2+} ions), q_e=1.6×10^{-19}C is the elementary charge, β is the damping coefficient (being within channels $\beta = \frac{E_m z q_e}{u_o} \cong 6.4z\times10^{-12}$ kg/s, with E_m (~10^7 V/m) the transmembrane electric field, and u_o=0.25 m/s the velocity of the ion through an open channel calculated from patch-clamp measurements of channel ion-currents). $\omega_o=2\pi\nu_o$ (ν_o the ion's oscillation self-frequency accepted to be equal to the recorded spontaneous intracellular ionic oscillation frequencies on the order of 0.1 Hz), $\omega=2\pi\nu$ (ν the frequency of the applied field) and E_o is the intensity amplitude of the applied oscillating field. Detailed calculations of the parameters are provided in Panagopoulos *et al* 2000 (144).

The right part of Eq. 2 is the force on the ion due to the applied E-field. The first term of the left part ($m_i\frac{d^2r}{dt^2}$) is the resultant force on the ion, the second term ($\beta\frac{dr}{dt}$) is a damping force and the third term ($m_i\ \omega_o^2\ r$) a restoration force exerted by the medium (144,145). While an oscillating ion close to the S4 sensors exerts gating forces on them, it receives zero opposite force, as the S4 charges are paired with opposite charges from adjacent helices of the channel (148). Eq. 2 is a second-order linear differential equation with constant coefficients, which is solvable once we know the values of the different parameters.

The general solution of Equation 2 (144) is:

$$r = \frac{E_o z q_e}{\beta\omega}\ cos\ \omega t + \frac{E_o z q_e}{\beta\omega} \tag{3}$$

The constant term $\frac{E_o z q_e}{\beta\omega}$ in the solution represents a constant displacement of the ion and has no effect on the oscillating term $\frac{E_o z q_e}{\beta\omega} cos\omega t$. This constant displacement represents a jump of the whole oscillation at a distance equal to the amplitude, in other words it doubles the amplitude $\frac{E_o z q_e}{\beta\omega}$ of the oscillation at the moment when the field is applied or interrupted. For pulsed fields (such as the vast majority of human-made complex RF/microwave EMFs, especially those employed in modern WC), this interruption/repetition occurs constantly with every repeated pulse. Therefore, pulsed fields are predicted to be twice as bioactive as continuous/non-pulsed fields of the same other parameters, and this explains a plethora of experimental findings showing increased bioactivity of pulsed compared with non-pulsed RF EMFs, which were previously unexplained (44,45,154, 155,157-159).

Ignoring the constant term in Eq. 3, the amplitude of the forced-oscillation is:

$$A = \frac{E_o z q_e}{\beta\omega} \tag{4}$$

An oscillating ion of charge zq_e (whose motion is described by Eq. 3) close to the S4 helices of a voltage-gated channel exerts a force F on the effective charge q of each S4, as described by Coulomb's law: $F=\frac{1}{4\pi\varepsilon\varepsilon_o}\cdot\frac{q\cdot zq_e}{r^2}$, ($r$ here is the distance of the oscillating ion from the S4). The ion displaced by dr during its oscillation, induces an additional force dF on each S4 sensor:

$$dF = -\frac{q\cdot zq_e}{2\pi\varepsilon\varepsilon_o r^3}\, dr \tag{5}$$

While in the case of a random/chaotic movement of the ion due to e.g. thermal motion $\lim\sum d\vec{r} = 0$, and $\lim\sum d\vec{F} = 0$, in the case of a coordinated polarized and coherent forced-oscillation, the sum force on each S4 from all four ions, is:

$$4dF = -2\frac{q\cdot zq_e}{\pi\varepsilon\varepsilon_o r^3}\, dr \tag{6}$$

The effective charge of each S4 domain is found to be: q=1.7q_e (161). The force on this charge exerted by a change of 30 mV in the transmembrane voltage required normally to gate the channel, is calculated to be (144): dF=8.16×10^{-13} N.

The displacement of one single-valence ion within the channel corresponding to this minimum force, according to Eq. 5 (for z=1, $\varepsilon \cong 4$, and r ~1 nm), is: dr=4×10^{-12} m.

The dielectric constant within proteins is significantly lower than in the aqueous solutions (4/80), and ion concentration in cells is of the order of 1 ion per nm^3 (144,147,148).

For 4 single-valence ions oscillating on parallel planes and in phase with an applied polarized (and coherent) oscillating field, the minimum displacement is (according to Eq. 6) reduced to: dr=10^{-12} m. The corresponding necessary displacement for ions outside the channel would be about 20-fold higher due to the higher dielectric constant of the aqueous solutions.

Thus, a crucial finding has been reached: Any external polarized and coherent oscillating EMF (like all technical/human-made EMFs) able to force mobile ions to oscillate with amplitude

$$\frac{E_o z q_e}{\beta\omega} \geq 10^{-12}\ \text{m} \tag{7}$$

is able to irregularly gate VGICs on cell membranes.

For z=1 (e.g. K^+ ions), and replacing q_e, β by their values in Condition 7, we get:

$$E_o \geq 0.25\nu\times10^{-3} \qquad (8) \qquad (\nu \text{ in Hz}, E_o \text{ in V/m})$$

For double-valence cations (z=2) (e.g. Ca^{2+}) the condition becomes:

$$E_o \geq 1.2\nu\times10^{-4} \qquad (9) \qquad (\nu \text{ in Hz}, E_o \text{ in V/m})$$

For pulsed fields (such as all MT/WC fields) the right part of Condition 9 is further divided by 2, becoming:

$$E_o \geq 0.6\nu\times10^{-4} \qquad (10) \qquad (\nu \text{ in Hz}, E_o \text{ in V/m})$$

It is clear that the amplitude of the forced-oscillation given by Eq. 4 is the critical parameter to determine the ability of a polarized/coherent EMF to induce biological/health effects. We shall name it 'Bioactivity of the EMF' or 'EMF-Bioactivity'. Thus:

$$\text{EMF-Bioactivity} = \frac{E_o z q_e}{\beta \omega} = k \cdot \frac{E_o}{\nu} \quad (11)$$

where $k = \frac{zq_e}{2\pi\beta} = \frac{u_o}{2\pi E_m} \cong 4\times10^{-9}$ C·s/kg is a constant quantity (depending upon the membrane electric field E_m and the velocity of the ion through an open channel u_o), E_o is the intensity amplitude and ν is the frequency of the applied electric field. We shall name k the 'bioactivity constant'.

Thus, a most reasonable and elegant result is reached, that the bioactivity of a polarized oscillating EMF is proportional to its maximum intensity (E_o) and inversely proportional to its frequency (ν), meaning that lower frequency fields are predicted to be more bioactive than higher frequency ones of the same intensity and waveform. Although this result was obtained considering the most usual/simple case of harmonically oscillating polarized EMFs, it is evident that non-harmonically oscillating polarized fields can also be approximately described in terms of their bioactivity by Eq. 11.

For pulsed EMFs with harmonically oscillating carriers, the amplitude doubles and so does the bioactivity:

$$\text{Pulsed EMF-Bioactivity} = 2k \cdot \frac{E_o}{\nu} \quad (12)$$

The same mechanism explains the biological action of polarized oscillating magnetic fields as well, if we replace in Eq. 2 the electric force $F_E=Ezq_e$, by a magnetic force:

$$F_B = B\, u\, zq_e \quad (13)$$

exerted on an ion with charge zq_e, moving with velocity u, vertically to the direction of a magnetic field of intensity B (in which case the magnetic force is maximum). In the simplest (and most usual) case of an alternating magnetic field $B=B_o sin\omega t$ with intensity amplitude B_o and based on the same reasoning as aforementioned, corresponding bioactivity conditions are obtained for an oscillating magnetic field.

For one single-valence ion moving through an open channel vertically to the direction of the applied magnetic field with $u=u_o=0.25$ m/s (the velocity calculated for ions moving through an open channel) (144) and for the case of a continuous oscillating magnetic field, the corresponding bioactivity condition is:

$$\frac{B_o u_o q_e}{\beta \omega} \geq 4\times10^{-12}\,\text{m} \quad (14) \quad (\omega \text{ in rad/s}, u \text{ in m/s}, B_o \text{ in T}),$$

from which is obtained:

$$B_o \geq 4\times10^{-3}\,\nu \quad (15) \quad (\nu \text{ in Hz}, B_o \text{ in T}), \text{ or}$$

$$B_o \geq 4\times10^{3}\,\nu \quad (16) \quad (\nu \text{ in Hz}, B_o \text{ in } \mu\text{T})$$

For double-valence ions the right part of Condition 16 is divided by 2:

$$B_o \geq 2\times10^{3}\,\nu \quad (17) \quad (\nu \text{ in Hz}, B_o \text{ in } \mu\text{T})$$

For double-valence ions and pulsing magnetic field the right part of Condition 17 is further divided by 2, and the bioactivity condition becomes:

$$B_o \geq 10^{3}\,\nu \quad (18) \quad (\nu \text{ in Hz}, B_o \text{ in } \mu\text{T})$$

It should be noted that apart from the drift velocity of the ion through the channel (u_o=0.25 m/s) that is accepted as initial velocity, the ion will acquire an additional velocity dr/dt due to the forced-oscillation. From Eq. 3, the following is obtained:

$$\frac{dr}{dt} = -\frac{E_o z q_e}{\beta} \sin \omega t \quad (19)$$

(or respectively: $\frac{dr}{dt} = -\frac{B_o u_o z q_e}{\beta} \sin \omega t$ for a sinusoidal magnetic field)

The corresponding magnetic force due to this additional velocity, $Bzq_e(dr/dt)$, is negligible (more than 10^8 times smaller) compared with the damping force $\beta(dr/dt)$, and thus, it is not taken into account in Eq. 2.

The maximum ($\frac{E_o z q_e}{\beta}$ or $\frac{B_o u_o z q_e}{\beta}$) of this additional velocity is independent of the frequency of the field (ω), and is much smaller for usual field intensities than the ion velocity through an open channel (u_o=0.25 m/s), which in turn is more than 10^3 times smaller than its corresponding average thermal velocity u_{kT} (168). Thus, the described ion forced-oscillation does not add to tissue temperature and this mechanism is 'non-thermal', in contrast to the known heating ability of the high intensity microwaves (128). The non-thermal nature of human-made EMF-bioeffects, including those of low power modulated/pulsing RF/microwaves, in contrast to high power microwaves, has also been discussed in previous studies (169,170).

This theory allows certain predictions for the bioactivity of some human-made EMFs widely present in the modern environment: For the sinusoidal alternating (continuous) 50-Hz E and B fields of high-voltage power lines with intensities of the order of E ~10 kV/m and B ~0.1-1 G (or ~10-100 μT) at close distances (10-20 m) from such lines the conditions 9 and 17 for double valence cations (e.g. Ca^{2+}) give: $E_o \geq 6\times10^{-3}$ V/m or $E_o \geq 6$ mV/m (which is satisfied by more than 10^6 times), and $B_o \geq 10^5$ μT, which is not satisfied, showing that the recorded effects from high-voltage power lines are due to the electric rather than the magnetic component of the resultant EMF, in contrast to what is usually considered. Thus, the electric component of power line EMFs is certainly capable of inducing biological effects in living organisms according to the mechanism presented, even for intensities down to 1-10 V/m, which exist in most homes and work places.

For the pulsing ELF E and B fields of MT/WC EMFs with a pulsing repetition frequency of ~100 Hz (3G/4G MT, DECT), E ~10 V/m and B ~1 mG (or ~0.1 μT) (30,40,54,55), the bioactivity conditions 10 and 18 respectively give: $E_o \geq 6\times10^{-3}$ V/m or $E_o \geq 6$ mV/m, which is satisfied by more than 10^3 times, and $B_o \geq 10^5$ μT, which is not satisfied for direct action, but it may be satisfied by the magnetically induced electric field, which is significant in this case due to the short rise/fall times of the pulses (143). Similar results are obtained for the 217-Hz pulsing E/B fields of 2G MT (30,40).

For Wi-Fi and Bluetooth wireless connections with a pulsing frequency of ~10 Hz, E ~1 V/m and B ~0.1 mG

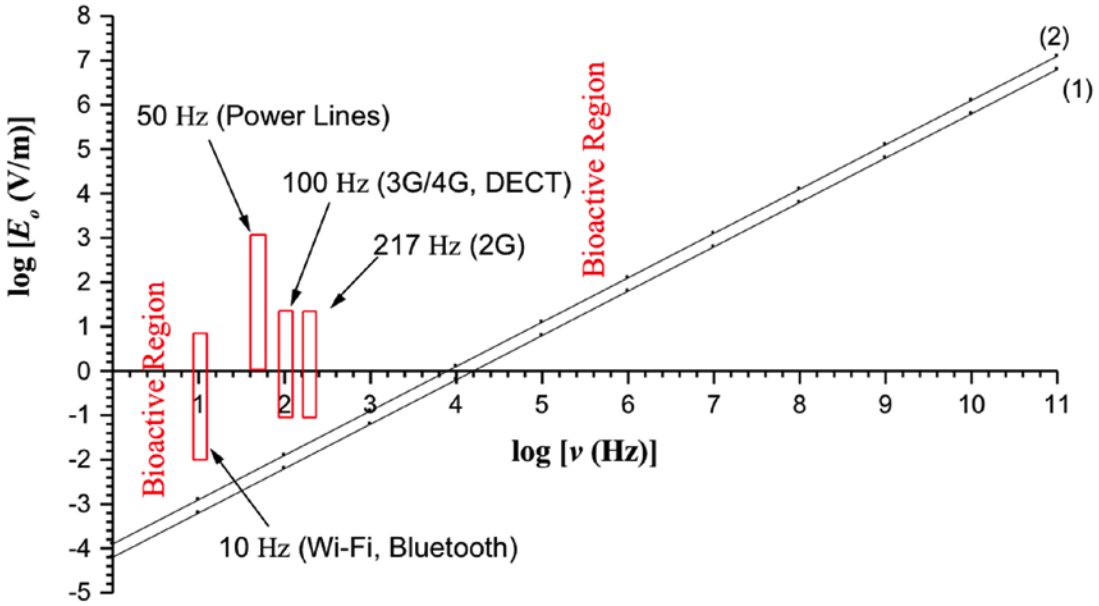

Figure 1. E-field bioactivity diagram showing the bioactive combinations of electric field intensity and frequency capable of inducing biological/health effects according to the ion forced-oscillation mechanism for dysfunction of voltage-gated ion channels in cells. The ELF electric fields of power lines, 2G/3G/4G MT, DECT, Wi-Fi and Bluetooth, are within the bioactive region (above lines 1 and 2). Line 1 refers to pulsed fields, such as the ELF pulsations of WC EMFs (Condition 10), while line 2 refers to continuous (non-pulsed) fields such as those from power lines (Condition 9).

(or ~0.01 μT) (171), the bioactivity conditions 10 and 18 respectively give: $E_o \geq 0.6 \times 10^{-3}$ V/m or $E_o \geq 0.6$ mV/m, which is satisfied by more than 10^3 times, and $B_o \geq 10^4$ μT, which is not satisfied for direct action.

The aforementioned numerical examples show that it is the electric field that seems to be the bioactive component of an EMF and not the magnetic field, in contrast to what has been considered before by health agencies (117). The magnetically induced electric field can also be bioactive in the case of ELF pulses of WC signals with short rise/fall times (143).

The bioactivity conditions 9 and 10 for continuous and pulsed electric fields respectively are depicted in Fig. 1. The region above line 1 (including the line) represents the bioactive combinations of intensity amplitude (E_o) and frequency (ν) for pulsed fields, and above line 2 (including the line) for continuous fields. The ELF electric field of power lines, 2G/3G/4G MT, DECT, WiFi and 'Bluetooth', lie within the bioactive region predicted by the presented theory.

3. Biochemical processes activated by irregular gating of VGICs, leading to DNA damage

Irregular gating of ion channels and ROS. Irregular gating of VGICs by oscillating polarized and coherent ELF EMFs as described [and originally in (143-146)] has been verified experimentally for calcium (Ca^{2+}), potassium (K^+) and sodium (Na^+) VGICs (172-174). This can alter intracellular ionic concentrations, disrupting the electrochemical balance of the cell and leading to DNA damage by OS/ROS overproduction (175-179).

Most ROS are free radicals. Free radicals are highly unstable molecules containing an unpaired electron, which is denoted by a dot ($^\bullet$), and have a tremendous tendency to chemically react with surrounding molecules and/or with each other in order to couple the unpaired electron and become stable. This is the reason why they have extremely short lifetimes. Most ROS react rapidly with surrounding biomolecules inducing chemical alterations (180). Overproduction of ROS in living cells due to EMF exposure has been reliably documented, with two important ROS found after EMF exposure being superoxide anion ($O_2^{\bullet-}$) and nitric oxide ($NO^\bullet$) (109). These may result in hydroxyl radical ($OH^\bullet$) and peroxynitrite ($ONOO^-$) correspondingly, both of which ROS are very reactive with biological molecules and specifically DNA, as discussed next. $ONOO^-$ may interact directly with DNA, as, similarly with $NO^\bullet$, it can be diffused everywhere in the cell (181). Superoxide anion radical ($O_2^{\bullet-}$) is catalyzed by superoxide dismutase enzymes in the cytosol or the mitochondria and is converted to hydrogen peroxide (H_2O_2) (109,182):

$$2O_2^{\bullet-} + 2H^+ \rightarrow H_2O_2 + O_2 \quad (20)$$

H_2O_2 is a critical molecule in oxidative damage since it can move to any intracellular site (including the nucleus), where it can be converted to the most potent $OH^\bullet$, which can damage any biological molecule, including DNA (183-187).

DNA damage by ROS leading to mutations and disease has been well studied (188,189). Pall (190), in a review of EMF-bioeffects studies with calcium channel blockers, noted a connection between voltage-gated calcium channels (VGCCs) and $NO^\bullet$/$ONOO^-$ overproduction. This verified earlier observations of EMF-induced effects on intracellular calcium concentrations, and the unique role of VGCCs (1,151-153,191,192).

It is known that the intracellular redox status can activate Ca^{2+}, Na^+ and K^+ channels in order to reinstate homeostasis (178), and inversely, activation of these channels determines the redox status and the electrochemical balance

of the cell (179). Multiple studies have found connections between the impaired function of calcium, potassium, sodium and chloride channels with the induction of OS and related pathologies (175-177). These studies provide additional evidence for the validity of the presented biophysical mechanism (143-146).

Calcium signaling and mitochondrial ROS production. Alteration of intracellular ionic concentrations will affect key cellular signaling pathways, including the Ca^{2+} signaling system, which regulates a variety of cellular functions including cell proliferation, differentiation, the ROS regulatory system and apoptosis (192-196). Impaired function of VGCCs in the plasma or in the mitochondrial membranes leading to critical changes in cytosolic or mitochondrial concentrations of Ca^{2+} ions, such as those following EMF exposure, is connected with pathogenesis and cytotoxicity (195,196).

Voltage-gated anion channels in the outer membrane of the mitochondria regulate Ca^{2+} entry into the intermembrane space and in the matrix, which is crucial for mitochondrial ROS production. Increased level of Ca^{2+} stimulates $O_2^{\bullet-}$ production by the electron transport chain in the mitochondria and/or activation of nitric oxide synthase (NOS), to generate more $NO^{\bullet}$. $NO^{\bullet}$ inhibits complex IV of the electron transport chain, triggering production of even more ROS (109,193). ROS overproduction in the mitochondria can damage DNA both in the mitochondria and the nucleus, and initiate a signaling cascade leading to apoptosis, as found in human spermatozoa after MT EMF exposure (36). Moreover, increased concentrations of $NO^{\bullet}$ in living cells due to activation of NOS at different locations of the cell may lead to formation of $ONOO^-$ (181,182).

Regulation of apoptosis is crucial for anticancer control (197). However, excessive apoptosis, induced by increased ROS levels, is connected with inflammatory diseases and cancer (198). When overproduction of ROS in a cell overloads the capacity of the antioxidant system of the cell, the cell/organism is under OS. This condition may lead to significant DNA damage with consequent genomic instability and carcinogenesis (182,183,194-198).

K^+ channels have also been shown to be involved in the activation of apoptosis (194), and voltage-gated Ca^{2+} and K^+ channels have been shown to be connected with cell proliferation and carcinogenesis (199). Thus, cytosolic concentrations of Ca^{2+} and K^+ ions play major roles in cellular function and metabolism. In addition, voltage-gated calcium and potassium channels play important roles in iron entry into the cells. Iron catalyzes the production of $OH^{\bullet}$ via the Fenton reaction and thus, impaired function of these channels can promote cellular toxicity (200-202).

NADPH oxidase and ROS production. Apart from the effect of EMFs on metallic cation voltage-gated channels (such as Ca^{2+}, Na^+ and K^+), proton (H^+) voltage-gated channels will be affected as well, as they operate in a very similar way (166,167). This in turn would affect the function of NADPH oxidase, a plasma membrane enzyme found in abundance in all cells, which normally generates ROS for the elimination of invading microorganisms (203,204). The activity of NADPH oxidase is strongly associated with H^+ channels and it may even act directly as a H^+ voltage-gated channel due to its $gp91^{phox}$ transmembrane subunit (205,206). NADPH oxidase generates an electron flux for the reduction of extracellular O_2 to $O_2^{\bullet-}$ (203,207).

NADPH oxidase is activated by cytosolic Ca^{2+} and possesses a Ca^{2+}-binding site in addition to its H^+ voltage-gated channel ($gp91^{phox}$ transmembrane region) (204). Thus, perturbation of intracellular concentrations of either H^+ or Ca^{2+}, after irregular gating of their voltage-gated channels, will affect the function of NADPH oxidase and trigger irregular ROS production.

NADPH oxidase has been reasonably suggested as a primary target of EMF exposure in living cells. In 2007, Friedman *et al* (208) found rapid ROS production in cultured cells after a few min of exposure to RF EMF emitted by a generator.

Na^+/K^+-ATPase and ROS production. Impaired function of Na^+, K^+, Mg^{2+} and Ca^{2+} voltage-gated channels may also affect the function of the Na^+/K^+ pump (ATPase) and Ca^{2+} pumps in the plasma membranes of all cells. The ion pumps (active ion transporters) across all cell membranes in coordination with the ion channels (passive ion transporters) determine the membrane voltage, the volume of the cell and the electrochemical balance (147,148). A positive-feedback amplification loop between Na^+/K^+-ATPase signaling and ROS production by the mitochondria was experimentally demonstrated in primary cultures of cardiac myocytes (209). Na^+/K^+-ATPase became a target for ROS-initiated signaling, and in turn, stimulation of Na^+/K^+-ATPase signaling function led to increased ROS production. This model can definitely be associated with dysfunction in living cells under EMF-exposure.

Therefore, it is clearly indicated that irregular gating of VGICs on plasma and intracellular membranes due to EMF-exposure will most likely trigger ROS overproduction and consequent cellular damage. Although plenty of data connecting ion channel dysfunction and the induction of cell death or cancer have been available for a long time (194,199), the connection between the dysfunction of VGICs and ROS overproduction (175-179,190-192) leading to DNA damage has not perhaps gained the attention it deserves.

Apart from action via ROS/free radicals, DNA damage may be brought about by irregular activation of DNases after alteration of intracellular ionic concentrations. Of the two forms of endonucleases implicated in the initiation of apoptosis, one of them is Ca^{2+}-dependent (DNase I). An increased level of intracellular Ca^{2+} in some cases is associated with increased apoptosis, possibly due to the activation of DNase I (210). Thus, the possible activation of DNase I by increased levels of intracellular Ca^{2+} may be an alternative way for DNA damage and related pathologies.

ROS and DNA damage. $OH^{\bullet}$ is considered the most potent oxidant of DNA. The main mechanism for $OH^{\bullet}$ production involves the iron-catalyzed conversion of H_2O_2 via the Fenton reaction (211): Fe^{2+} is oxidized by H_2O_2 to Fe^{3+}, producing an $OH^{\bullet}$ radical and a hydroxide ion (OH^-) (Eq. 21). Fe^{3+} is then reduced back to Fe^{2+} by another molecule of H_2O_2, producing a hydroperoxyl radical and a proton (Eq. 22).

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\bullet} + OH^- \quad (21)$$

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HOO^{\bullet} + H^{+} \quad (22)$$

The net effect is the conversion of two hydrogen peroxide molecules to produce two different oxygen-radical species, with water ($H^+ + OH^-$) as a byproduct.

$$2H_2O_2 \rightarrow OH^{\bullet} + HOO^{\bullet} + H_2O \quad (23)$$

The $OH^{\bullet}$ radical reacts with any biological molecule in its immediate environment, including DNA. For example, it can break macromolecules (R-R or R-H) or abstract atoms from them (such as the various hydrogen atoms of the deoxyribose) by breakage of covalent bonds. This results in chemical alterations of the macromolecules and production of new free radicals ($R^{\bullet}$ or $RO^{\bullet}$):

$$R\text{-}R + OH^{\bullet} \rightarrow ROH + R^{\bullet} \quad (24)$$

$$RH + OH^{\bullet} \rightarrow R^{\bullet} + H_2O \quad (25)$$

$$\text{or } RH + OH^{\bullet} \rightarrow RO^{\bullet} + H_2 \quad (26)$$

The new free radicals will further react with other molecules resulting in additional chemical alterations. Corresponding evidence for DNA damage by $ONOO^-$ is available as well (181).

In conclusion, there is a clear sequence of events starting from the irregular gating of VGICs by EMFs up to DNA damage and related pathologies, including carcinogenesis.

4. Discussion

The present study reviewed experimental and epidemiological findings connecting exposure to purely ELF, and RF (containing ELF) human-made EMFs, with DNA damage and related pathologies, including cancer. It is documented that both such types of human-made EMF-exposure can induce OS (3,34,36-39,43,45,109), DNA damage (1-55,84,85) and infertility (56-71). It is also documented that the same types of EMF-exposure are linked with increased cancer risk both in humans and experimental animals (72-83,86-98,110-114).

We attempted to provide a complete, plausible explanation of these DNA damage-related findings on a biophysical and biochemical basis. According to the ion forced-oscillation mechanism for dysfunction of VGICs (143-146), human-made (polarized and coherent) ELF/ULF EMFs or the ELF/ULF modulation/pulsing/variability components of modern RF/WC EMFs can alter intracellular ionic concentrations by irregular gating of VGICs on cell membranes. This leads to immediate OS by ROS (over)production in the cytosol and/or the mitochondria, which can damage DNA when cells are unable to reinstate electrochemical balance (normal intracellular ionic concentrations). Consequently, DNA damage can lead to reproductive disabilities, neurodegenerative diseases, aging, genetic alterations and cancer.

According to the presented biophysical mechanism, the bioactivity of a polarized/coherent EMF is proportional to its intensity, inversely proportional to its frequency and doubles for pulsed fields, meaning that the ELF/ULF EMFs and even more the pulsing RF EMFs with ELF pulsations such as all WC EMFs, are predicted to be the most bioactive. This explains the recorded effects of purely ELF EMFs (1-5,9,13-18,22,47,50,72-82,117,212) and those of modulated/pulsing/variable RF EMFs (1,3,4,6-8,19-21,23-46,48,49,51-55,57-71,84-107,109-114,118,121-126). As emphasized, all types of RF exposure from all types of antennas and WC devices (WC EMFs) necessarily combine RF carrier signals with ELF/ULF components in the form of pulsing, modulation and random variability. The RF carrier signal alone does not contain information. The information is always contained in the ELF signals that modulate the RF (4). Significant experimental evidence shows that the bioactive parameters in a complex signal are its ELF components, and that non-modulated and non-pulsed RF signals alone do not usually induce biological effects (4,44,45,151-159), apart from heating when they possess high enough frequency and intensity (128,168-170). Therefore, the present study suggests that the vast majority of non-thermal effects attributed till now to various types of RF EMF-exposure, are actually due to their ELF/ULF components.

The presented biophysical mechanism and the provided numerical examples show that it is the direct ELF electric fields (and the magnetically induced electric fields in the case of sudden pulses), not the magnetic, that are the bioactive components, in contrast to what has been considered before by health agencies (117), and in agreement with previous experimental findings (191). Although electric fields are less penetrating in living tissue than magnetic fields, penetration depends upon the inverse square root of frequency, and thus ELF electric fields are significantly penetrating. Penetration depends also upon the inverse square root of the medium conductivity (213). Even though seawater is much more conductive than living tissue, ELF electromagnetic waves (thus both the electric and the magnetic parts of the waves) are penetrating several meters into seawater, accommodating communications with submarines (214). Moreover, it is known that isolated tissues respond to externally applied pulsed or sinusoidal ELF electric fields at very low thresholds (~10^{-3} V/m) similar to those predicted by this theory (143,215-217). This evidence shows that ELF electric fields penetrate enough to induce effects into living tissue, even at very low field intensities. Finally, skin cells, nerve terminals, eyes and organs close to the surface, such as the brain and heart, are directly exposed to externally applied EMFs. For all these reasons, no distinction is made between externally applied ELF electric fields and internally induced ones.

The ion forced-oscillation mechanism/theory was described in the present study by realistic equations based on the forces exerted on mobile ions in the vicinity of the voltage-sensors of VGICs on cell membranes by externally applied human-made (polarized) EMFs. The solution of the basic Eq. 2 resulted in bioactivity conditions connecting the intensity of an applied polarized EMF with its frequency. The bioactivity conditions 8-10, and 16-18, provided the bioactive intensity-frequency combinations for continuous and pulsed electric and magnetic fields. The final numbers explain almost all the experimental and epidemiological findings connecting biological/health effects with human-made EMF-exposure.

Although the mechanism was first published in 2000 (144) based on the available data on the structure and function of the

VGICs, newer details on the roles of S1-S6 helices, channel structure, relaxation, hysteresis and gating, have not refuted but verified and extended that knowledge (162,163,165,218-221).

What is more difficult to explain is the existence of non-linear phenomena such as the increased bioactivity 'windows' reported occasionally in the EMF-bioeffects literature, where certain effects are intensified within certain values of an EMF-exposure parameter (intensity in most cases, or frequency) (1,40,151-153,222). The existence of 'windows' shows that the response of living cells/organisms to EMFs is not generally proportional to the aforementioned EMF-parameters. Non-linear responses of living cells have not been explored in depth and it will take a number of years until they are. A possible explanation of observed intensity 'windows' according to the described mechanism has been suggested as being due to an existing upper limit in the membrane gating voltage change (222). Indeed, such an upper limit seems to exist. The VGICs respond to membrane voltage changes from ~30 mV (minimum) to ~100 mV (maximum) where the conductivity of the channel saturates (218,221). Apart from this possible explanation, no other explanation for the observed 'window' effects has been provided so far.

An effect not included in the bioactivity Eqs. 11 and 12 is the increased bioactivity of highly and unpredictably varying exposure such as those from WC devices (including mobile phones and Wi-Fi) and corresponding antennas (4,121,122). The described mechanism results in accurate predictions when the applied EMFs have constant parameters (intensity and frequency, among others). When the parameters are highly and unpredictably variable, the mechanism, and any possible mechanism, can only estimate effects according to the average and maximum exposure values of the varying EMFs. Finally, the bioactivity equations include field (and tissue) parameters and not exposure variables such as exposure duration or intermittence, which are also very important (16,17,19,41,55,122). One way to include such parameters is to multiply the right parts of Eqs. 11 and 12 by certain coefficient(s), which would be estimated experimentally. This could be a subject for future development of the theory.

This theory has successfully explained for the first time the sensing of upcoming earthquakes by animals, and the sensing of upcoming thunderstorms by sensitive individuals through the action of the partially polarized natural EMFs associated with these phenomena (146,223).

Any 'mechanism' in science (particularly in physics) must be based on simple and reasonable postulates, and must necessarily be expressed quantitatively (by solvable equations and numbers). The values of the different parameters in the equations must be based on physical/molecular data. Qualitative descriptions alone or incomplete quantitative descriptions based on incomplete or unsolvable equations do not constitute a 'mechanism'. The presented biophysical mechanism (143-146) is the only one that fulfills the aforementioned criteria in the case of EMF-induced bioeffects. Previous important attempts on mechanisms focusing on ions moving inside membrane channels or other proteins (224-227) were not successful, mainly for the following reasons: i) They had not taken into account damping and restoration forces (224,226), or did not calculate them (225,227). The difficulty was not related with considering such forces, as this is standard in oscillation mechanics, but with calculating their parameters such as β and ω_o, or the maximum velocity of the ion (u_o) within a channel. ii) They did not consider coordinated motion of several ions oscillating in parallel and in phase due to polarization and coherence, exerting additive forces on channel sensors, which prevail against the greater but chaotic forces due to the random thermal motion of the ions. iii) They focused on magnetic fields and magnetically induced electric ones, and ignored externally applied electric fields, which eventually seem to be more bioactive (191). iv) They did not result in numbers for field intensity versus frequency necessary to affect cells, although some experimental reports have indicated bioactive frequencies close to those predicted by Liboff's ion cyclotron resonance (ICR) model (224,228), possibly indicating some additional/secondary resonance mechanism involving ICR phenomenon (169). v) Apart from the study by Balcavage *et al* (226), there was no focus on the gating of VGICs, which is by far a more probable event to initiate biological effects, but simply on the motion of ions within channels/proteins.

Several other suggestions on possible mechanisms also face problems on fundamental issues (229-231). What is termed by Pall 'VGCC activation mechanism' and presented as his own discovery is none other than the mechanism presented here. A commentary paper/letter to the editor was published on this major ethical issue (129). An extended review of suggested mechanisms has been written by Creasey and Goldberg (169).

It has been claimed that the ELF components of complex RF-ELF EMFs of WC need to be 'demodulated' in order to be sensed by living organisms (232). 'Demodulated' or not, the fact is that the ELF components of modulated/pulsed WC signals can be directly sensed by both ELF meters/spectrum analyzers and living organisms (40,55).

Although there have been successive publications of this mechanism since 2000 (144), the subject is of great importance and in each consecutive publication additional important aspects are elucidated and/or refined. In our previous study in 2002 (145), the mechanism was extended to include oscillating magnetic fields and the thermal noise problem was discussed in more depth, while in 2015 (143) the mechanism was applied to reveal the importance of polarization/coherence in the bioactivity of man-made EMFs. In 2017 (223) and 2020 (146), it was applied to explain the sensing of upcoming thunderstorms and earthquakes, respectively, by sensitive humans/animals. In the present study, several aspects are further refined, including: i) The distance of S4 sensors from the channel pore; ii) more details on damping coefficient β and bioactivity constant k (Eq. 11); iii) further explanation of the role of the constant term in the solution (Eq. 3); iv) the similarity of proton voltage-gated channels with the other VGICs; v) numerical examples demonstrating the ability of the pulsing ELF electric and magnetic fields of 2G/3G/4G MT, DECT, Wi-Fi, Bluetooth, and the power line ELF fields to induce biological/health effects; vi) the velocity of oscillating ions; vii) bioactivity diagram extended to intensities down to 10^{-5} V/m; and viii) discussion on other suggested mechanisms.

Moreover, the present study documented how the impaired function of VGICs on the membranes of living cells triggers (over)production of free radicals/ROS, such as the most potent

$OH^{\bullet}$ produced by H_2O_2 via the Fenton reaction, and $ONOO^-$ produced by $NO^{\bullet}$. These are considered the main damaging species for DNA and other critical biological molecules. It is estimated that approximately two-thirds of the DNA damage caused by ionizing radiation is due to $OH^{\bullet}$ (233,234). Although $OH^{\bullet}$ can only diffuse at distances comparable to the length of a macromolecule, H_2O_2 can move to any intracellular site. Thus, even though the most potent $OH^{\bullet}$ due to its high reactivity has an extremely short lifetime (of the order of 10^{-9}-10^{-4} s depending on the presence of other molecules) it can be formed by H_2O_2 at any location within the cell (including the nucleus) and act instantly upon DNA or other macromolecules (233,234). As for $NO^{\bullet}$/$ONOO^-$, they can be diffused anywhere in the cell and thus directly affect any molecule, including DNA (181). Even though the present study identified specific pathways of ROS overproduction or the release of DNases connected with disrupted ionic concentrations in EMF-exposed cells, the exact molecular mechanisms need to be further explored and elucidated.

Finally, the present study discussed how unrepaired/misrepaired DNA lesions/damage such as strand breaks, covalent bond breakage or nucleotide base damages, lead to cell senescence, cell death or mutations, and related pathologies, including cancer. Even though effective mechanisms have evolved in all animals/cells for repairing DNA damage induced by environmental stressors, it is very different when the damaging events are isolated or random (e.g. radioactive particles or γ-photons of cosmic/natural radioactivity, or sporadic x-ray diagnostic exposure), compared with persisting/repeated exposure to cytotoxic agents, even when these agents are relatively weaker. Exposure to human-made EMFs and especially to the most detrimental ones from WC antennas/devices and high-voltage transmission lines (4) has become a new reality in modern life. Billions of people are exposed to such EMFs on a daily basis. Although they are less cytotoxic than radioactivity or certain cytotoxic chemicals, they represent the most persistent daily cytotoxic stressors against which any repair mechanisms cannot be efficient enough. By contrast, previously existing cytotoxic agents expose us randomly as isolated events. When an organism is constantly under OS due to a totally new cytotoxic agent such as human-made EMFs, no protective mechanism, evolved in the billions of years of biological evolution to protect from natural (non-polarized) EMFs/radiation or isolated hazardous events, can be effective enough.

The repair capability of cells in response to DNA damage is crucial for the final outcome. The threshold of damage above which it becomes irreparable depends on cell type and the health and status of the organism. An organism with poor health and/or under stress and inflammation due to OS is expected to have decreased repair capability and increased cancer risk. Epigenetic effects such as altered gene expression may also lead to cellular dysfunction and carcinogenesis (133,235,236).

Both DNA damage and alterations in protein synthesis, especially increased levels of stress proteins, are reported to be induced similarly by both ELF and pulsing RF EMFs (237,238). However, the effects of pulsing RF were attributed to the carrier frequency, and it was not considered that perhaps in both cases (ELF and pulsing RF) the ELF components might be responsible for the effects, as suggested now by the present study.

To the best of our knowledge, the present study provides for the first time a complete and precise biophysical/biochemical picture to explain the great number of experimental and epidemiological findings connecting human-made EMF exposure with DNA damage and related pathologies such as cancer, infertility and neurodegenerative diseases.

The long-existing experimental and epidemiological findings connecting exposure to human-made EMFs and DNA damage, infertility and cancer, are now explained by the presented complete mechanism. The present study should provide a basis for further research and encourage health authorities to take measures for the protection of life on Earth against unrestricted use of human-made EMFs.

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Availability of data and materials

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Authors' contributions

DJP designed the study and wrote the main manuscript. AK verified all equations and calculations. IY coauthored section 3 on biochemical processes. GPC reviewed and evaluated all data. All authors have read and approved the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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