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Volume Transmission in the PathophysiologyofDelirium

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ABSTRACT:

Delirium is a neurobehavioral syndrome marked by disturbances in cognition, attention, memory, perception and sleep-wake cycle which is common in hospitalized elderly. Although it is one of the oldest conditions known to medicine, its pathophysiology remains poorly understood. Since currently there are no preventive therapies for delirium, elucidation of cellular and molecular underpinnings of this condition may lead to the development of early interventions and thus prevent permanent neurologic damage.

Phylogenetically, many neurotransmitters relevant to modern neurology and psychiatry have been present in primitive organisms prior to the existence of a nervous system. Ontogenetically, several neurotransmitters, including acetylcholine, are present before synaptogenesis or neurogenesis, suggesting an alternative communication platform than synaptic transmission.

In this article we make the case for the role of volume transmission in the CNS physiology and pathology. This is a signaling modality which engenders a slower but widespread type of information processing, different than the quick point-to-point synaptic-based one. Volume transmission may be responsible for mass-sustained signaling which engenders the states of awareness, cognition or wakefulness, known to "wax and wane" in delirium. Understanding, therefore volume transmission and the information processing fathomed by it may lead us to a better grasp on the pathophysiology of this condition.

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INTRODUCTION

Volume transmission (VT) representsanon-synaptic mode of intercellular signaling in the CNS in which the transfer of information is mediated by diffusion of neurotransmitters through the extracellular space (ECS). The journey of signaling molecules through the brain parenchymais dependent on the expression of aquaporin-4 (AQP-4) water channels on astrocytic membranes and the geometry of the ECS.

VT is relevant to delirium because, unlike synaptic communication, it is as low and wide spreadsignaling platformbettersuited forpervasiveCNS functionssuch asarousal,attention,mood,cognition and circadian rhythm.Thesefunctionsareoften impairedin delirium. In addition,mostneurotransmitters believed tobeaffectedin delirium,such asmonoamines,acetylcholine,glutamate, endogenousopioids, GABA,aswellaschemokinesand cytokinesare volumetransmitters.

Neuroinflammation,apossiblepathoetiologicalmechanism ofdelirium,ischaracterizedbyexcessive glutamatereleasein theECSand astrocyte edemaatthe expenseoftheECS volume(1).ReducedECS impairsVTofmultipleneurotransmittersystems,possiblyresultingin symptomsofdelirium. Erythropoietin (EPO)

wasshown toreversethetoxiceffectsofglutamateintheECSbydown-regulating AQP-4receptors,decreasingastrocyticedema,and normalizing theECS fluid homeostasis. NonerythropoieticvariantsofEPO,such asasialoerythropoietin,may proveto be valuabletherapeutic additionstothearmamentariumofdeliriumtherapies.

Volume orwired transmission: the soupsorthe sparks

Whetherneuronscommunicatewithoneanotherelectrically(sparks) orchemically(soups)wasa matteroffiercedebate in theearly 1900s. In1921, withOtto Loewi'sdiscovery ofthe"Vagusstoff" (laternamedacetylcholine),theconceptoftheneurotransmitterwasborn(2). By the1980sitbecame clearthatnot onlyneurons,butallCNS cellscommunicatewith each otherbyreleasingsignaling moleculesinto theECSofthebrain. Thisgavebirthtotheconceptof volumetransmission (VT)(3).

VT wasdescribedasacommunication platform among brain cellsinwhich signaling moleculesdiffuse through theECS with theflowoftheinterstitialfluid(ISF)and/orcerebrospinalfluid (CSF)to actupon non-synapticreceptorssituatedatadistancefrom thesourceofthesignal(3). Thisconceptreceived limitedattention in psychiatryin spiteofthefactthatmostneurotransmittersrelevantto neuropsychiatricdisorders,including monoamines,acetylcholine (4),glutamate (5),endogenous opioids (6),GABA(7),as wellaschemokinesand cytokines(8)areknownvolumetransmitters.

In thepastthreedecades,clinicaland preclinicalstudieshavedemonstrated thatin addition tosynaptic or wired transmission (WT),occurring among neuronalpopulations,thebrain cellssuch asglia, endothelialcellsofmicrovesselsandpericytescommunicatewith each otherandwith theneuronsby releasingsignaling moleculesintotheECS,a commonmodeofcommunicationamongcellsthroughout mostbodytissues.

Thetwo modesofcommunicationintheCNS,WTand VT,presentwith differentsignaling characteristics.WTenablesfast,selectiveand focusedCNS functions,such asthoserequiredforplaying piano,practicingsports,ordriving avehicle(9)(10). On theotherhand,signaling byVTistemporally slower,broaderin reach,affecting large volumesofbrain tissuein awidespreadmanner(9)(10).This modeofsignaling isbettersuitedforenabling pervasiveandmass-sustained brain functionssuchas arousal,attention,cognition,mood,appetite,and circadian rhythm(11).Interestingly,thesearealso theCNS functionsaffectedin delirium.

VTismadepossiblebythecirculationofECSfluid viaAQP-4waterchannelsexpressedon perivascular astrocyticend-feet.Theflow ofCSF andISFfacilitatesboththediffusionofneurotransmitters through thebrain parenchyma andtheclearance ofmolecularwaste,such asbetaamyloidand othermisfolded proteins.Down-regulationofAQP-4receptors on astrocytespredisposestothepericellular accumulationoffluid and ECSswelling. Up-regulationofAQP-4receptorsfacilitatesthefluid entryinto theastrocytes,causing astrocyticedemaandECSshrinking(12). A desiccated ECS withlossoffluidflow facilitates stagnation andaccumulationofmolecular waste whichmaypredisposeto neuroinflammation. Adequateexpression ofAQP-4 channels on astrocytic end-feetisessentialfortwo functions:loweringthesusceptibilitytoneuroinflammation andenabling physiologicalfluid fluctuationsduring sleep and wakefulness(13)(14). Recentstudiesdemonstrated thatup-regulation of AQP-4receptorsinducesapro-inflammatorystate,manifested byastrocytosisand microgliosisaswell asimpairmentoffluid homeostasis(15)(16).

A bodyof evidencegoingasfarbackas1980demonstratesthattheECSfluidvolumefluctuateswith thelevelofneuronalactivity. Forexample, during information processing (usuallyduring theday)the ECS decreasesinsize,asthefluid ispumped out.During sleep,theCSF gushesinviaAQP-4receptors, swelling theECS.Thistidalwave ofECSfluid washesthemolecular wasteproduced bythesynaptic activitythroughout thepreviousintervalof wakefulness(17)(18)(19).Thecircadian pattern ofsignaling byVTreflected inthedailyfluctuationsoftheECS volumemay engenderhuman chronobiological rhythms,such as arousal,attention,cognition ormood. PathologicalvariationsofECSvolumewith accompanying patternofsignaling (inneurotransmittersystemsutilizing VT)may manifestclinicallyas fluctuationsinthelevelofawarenessfrequentlyseenin delirium.

Table1. Extracellularspace volumeand fluid circulation

IncreasedECS volume	Decreasedastrocytic volume	Sleep,clearance ofmolecular waste	Down-regulationof AQP-4receptors	Anti-inflammatory state
DecreasedECS volume	Increasedastrocytic volume	Wakefulness, accumulationof molecularwaste	Up-regulationof AQP-4 receptors	Pro-inflammatory state

Volume transmittersand delirium

Receptormappingevidenceobtained overthepastthreedecades,utilizingautoradiographyand immunochemistrydemonstratesthatsome neurotransmittersystemssignalalmostexclusivelyviaVT, whileothersutilizeboth WTand VT(20)(9). ItwassuggestedthatWTand VT maybecomplementary modesofcellularcommunicationandthatcellularnetworksmayswitch from onetothe other depending onthetypeofinformation processing they engagein(21).

Theimportance ofacetylcholine(ACh)in delirium wasextensivelydocumented bymultiplestudies, howevertheroleofacetylcholinevolumetransmissionin thisdisorderhasbeenemphasized lessoften eventhough86–93%ofthecholinergicboutonsintheCNSdo notmakesynapticcontact,releasing ACh directlyinto theECS(4)(9).Untilrecentlyitwasbelievedthatthediffusion ofthisneurotransmitter to distantnon-synaptictargetswasunlikelybecause of thepresenceofACh-degrading enzymes acetylcholinesterase(AChE)and butyrylcholinesterase(BuChE)in theECS.Recently,howeverastudy demonstrated thatACh coulddiffuseto considerable extracellulardistancesin spite ofAChEand BuChE because ofthehigh extracellularconcentrationsofACh-synthesizing enzyme,choline-acetyltransferase (ChAT). Thisenzymeisableto manufactureACh locally,thusenablingitslong distanceVTat physiologicalECSconcentrations ofAChEand BuChE(22).

Glycineand glutamateneurotransmittersystemsweredemonstratedtoutilizeboth,VTand WT signaling (5)(23).Thestudyofglutamatedynamicsin theECSwasmadepossiblebytherecent developmentoffluorescent visualizationtechniques.With thehelpofthesenovel toolsitwaslearned thattheECS glutamate originates eitherfromsynapticspill-overorfrom releasebythe astrocytes (24). In theECS,glutamateacts upon non-synapticionotropicreceptors(AMPA,kainateand NMDA)and type I mGluRs(25).Non-synapticmGluRsIwerefound toplayakeyrolein dendriticinformationprocessing,
suggesting thatglutamateVTisessentialfortheCNScomputation(26)(27). Glutamatemaybecrucial to thedevelopmentofdeliriumbecauseitachieves high extracellularconcentrationsduring neuroinflammation.Chemokinesproduced bymacrophages migrating into theCNStriggerglutamate releaseinto theECS alongwithup-regulation ofAQP-4receptorson astrocyticend-feet, resulting in astrocytic edemaand desiccationoftheECS,possiblyengendering delirium-likesymptoms(1).

Monoaminesarereleasedin theECSto diffusewith theflowoffluid todistanttargets(27).Preclinical studiesdemonstratethat 94%oftyrosinehydroxylase-positiveboutonsinarea10oftheprefrontal cortexhavenoidentifiablesynapticstructures(28).Interestingly, NEsignaling byVTfacilitatesthe circadian ejectionoffluid from theECS,during wakefulness. In arecent study,micetreatedwithNE blockersshowed both,signs ofsleepinessandincreased ECS fluid volume,onMRI,suggestingadirect relationship betweenNE modulationoftheECSvolumeand thephysiologyofsleep(15).

GABAisreleasedbyastrocytes into theECSviabestrophin 1channels(29)(30). ThepathologyofGABA VTmaybecomeclinicallymanifestwhenthe ECSfluid volume isreduced,resulting in high extracellular concentrationofthisneurotransmitter.Thismayexplainthehypersensitivityofdeliriumpatientsto the effectsofGABA-ergicdrugs.

Pro-inflammatorycytokinessuch asinterleukin1betaand tumornecrosing factoralphaareproduced bythereactiveastrocytesand microglia. Thesecytokinesareexclusive volumetransmitters with documented involvementinsleep physiologyandthepathologyofneuroinflammation(31)(32).

Beta-endorphin'slong distancediffusion alongwith theflowofISF andCSFwasestablished bymultiple studies(33)(34)(35).Thisneurotransmitterwasshown to modulatewidespreadCNS functionssuchas arousal,feeding,learning,sexualbehavior, pain and reward(25)(10). A reduction oftheECSfluid volume mayresultinexcessivelevels ofbeta-endorphins,perhapsmanifestedclinicallyasfluctuating confusion.A recentstudyfound increased circulating levelsof betaendorphin and cortisolin postoperativedelirium(36).

Apathophysiologicalmodelofdelirium:go-with-the-flowtoxicity hypothesis

Wehypothesizethatreduced ECSvolumeresultsinhigh extracellularconcentrationsofmolecularwaste productsand diffusing neurotransmitters.Bothmayresultindeliriumbyimpairingsignaling byVTin neurotransmittersystems which engender widespreadand pervasive CNS functionssuch as arousal, attention,mood,cognitionand circadian rhythm. Wehypothesizefurther thatexogenously
administered drugsmayinteractwith thehighlyconcentratedvolumetransmittersin thereduced ECS, resulting in agonisticortoxic effectsmanifested clinicallyasdelirium.

Following isaproposed stepwisepathophysiologicalmodel ofdeliriumtriggered bytheperipheral inflammation,such asinfectionorsurgery(37),leading toneuroinflammation andimpairmentof signaling byVT:

1. In responsetoperipheralinflammationmacrophagesmigratetotheCNS andrelease chemokines(locallyactingcytokines)whichinhibitglutamatetransporter-1(GLT-1)protein in astrocyticend-feet,leading to elevatedconcentrationofglutamatein theECS(38)(39)(40).

   Physiologically,theextracellularglutamateisregulated byafamilyofglutamatetransporters, including GLT-1and GLT-2 whicharepredominantlyexpressed on astrocytes(41). Interestingly, it wasdemonstratedthatGLT-1 mayformfunctionalcomplexeswithAQP-4waterchannelsand possiblywitherythropoietin receptors(EPOR)which arealsofound in astrocyticend-feet (42)(43).

2. Extracellular glutamate,acting onnon-synapticmGluRstype I,increaseswaterpermeabilityof astrocyticend-feetbyup-regulatingAQP-4channels,leading to astrocyticedemaand neuroinflammation(44).

   Neuroinflammationmaybeadirectresultofastrocytic edema,ormaybetriggered bythe accumulationofmolecularwastein theECS.

3. Edematousastrocytesalong withneuroinflammationcontribute tolocalcellularcrowdingatthe expenseoftheECS volume(46)(47).

4. ReducedECSfluid volumeand flowcontributes tobuild up oflargeconcentrations ofvolume transmitters,such asdopamine,NE,GABA,betaendorphin,cytokinesorcortisolas wellas molecularwaste,likeimproperlyfolded proteins,impairing VT of multipleneurotransmitter systems,resulting inthefluctuatingsymptomsofdelirium(45).

TheconceptofVTin thecontextofreduced ECS fluidvolumemaychangethewaywethinkaboutthe actionofdrugsin delirium.Aftercrossing theblood-brain-barrier,mostpharmacological compounds diffusethroughouttheECS and readilyaccessnon-synapticreceptors. Thesereceptorsarenotonly morenumerousthanthesynapticones,buttheyweredemonstratedto havehigheraffinityforligands, leading to thesuggestion thatpsychotropicdrugsmaynotreach synapticreceptorsatall,butexerttheir actionon non-synapticreceptors exclusively(25).

UnderpathologicalcircumstancesoflowECSvolumeand high concentrationsofvolumetransmitters (such asinflammationorischemia), theexogenouslyadministered drugsmayinteractintheECS with diffusing agonisticneurotransmitters,resulting in additiveadverseeffectsortoxicity,whichmay manifestassymptomsofdelirium.Thismechanism mayexplain,forexample, deliriuminduced by low lithiumlevelsfrequentlyseen in elderlyillpatients. Other examples mayincludetheECS interaction betweenbenzodiazepinesand thevolumetransmitterGABA, engenderingconfusion,oropiatedrugs and theendogenous volumetransmitterbeta-endorphin,causing variousdegrees oflethargy.

Extensiveliteratureexists aboutdopaminergicdrugs,lithium, opiatesand benzodiazepinespredisposing todelirium(48),however thefactthattheymayreach high concentrationsin thedesiccatedECSand interactthere withdiffusing agonisticneurotransmitterswas,perhapsgiven lessthought.

Erythropoietinand aquaporins: ofblood and water

Erythropoietin (EPO)isahematopoieticgrowth factorproduced inthekidneyand fetalliver. EPOisalso produced in theCNSasa cytokinereleasedbyvariousnon-neuronalcellsinto theECSwhereitdiffuses with the fluid flow. Overthepastdecade,EPOwasfound to haveneuroprotectiveproperties dependenton geneactivationwhicharecompletelyindependentfromitserythroid effects(49).Inthe pastfewyearsan immediateactionofEPO,independent ongeneactivation,and unrelatedto neuroprotectionwasdemonstrated. Itconsistsofblockingextra-synaptictype ImGluRs,preventing AQP-4up-regulation.ThisactionistriggeredbyEPObinding toerythropoietin receptors(EPOR) on astrocytic end-feetwith theimmediateeffectofrestoringfluid homeostasisintheECS(50)(51).The anti-inflammatoryactionofEPOistwofold:direct,relatedtolowering extracellularglutamate,and indirectbydown-regulation ofAQP-4receptorsand reductionofastrocyticedema. Both pathways blockreactiveastrocytosisand microgliosis,and inhibitthepro-inflammatorycytokines (demonstrated byblocking lipopolysaccharideinduced cytotoxicity)(52).

Recombinanthuman erythropoietinwasfound to betherapeuticinseveralCNS disordersincluding ischemicstroke,mechanicaltrauma,experimentalautoimmuneencephalitis,subarachnoid hemorrhage,

seizuredisorderand neurodegenerativedisorders.Arecentstudyin ratsdocumented thatif administered systemicallyup to 3hoursaftercerebralarterialocclusion,EPOreducesinfarctionvolume by75%(53).

Thesafetyofhuman recombinanterythropoietinwasdemonstrated bymorethan adecade of widespreadclinicaluseand preclinicalinvestigations(54)(55). To ourknowledge,EPOor nonerythropoieticvariantsofEPOwereneverstudiedin delirium,in spiteoftheirfavorableactionon extracellularglutamateand AQP-4receptors. Nonerythropoieticvariantsof EPO,such as asialoerythropoietin,maybe idealcandidatesforclinicaltrialsin delirium becausetheyreadilycross theblood brain barrierand lackthe effectsonred cellmassorplateletsaggregability occasionallyseen with erythropoieticvariants (56).

Conclusions

Widespread CNS functionssuch asarousal,attention,mood,cognition andcircadian rhythm,frequently affectedin delirium,arebelieved tobe mediatedbyVT. Majorneurotransmittersystemsinvolvedin thepathoetiologyofdeliriumareknownfortheirnon-synapticreceptorsandtheabilitytorelease signaling moleculesinto theECS.Pathologicalreduction oftheECS fluidvolume predisposesto increased concentrations ofvolumetransmitters which in combinationwithexogenouslyadministered agonisticdrugsmayleadtoadditive toxiceffects. Understandingfluid homeostasis, neuroinflammation,andVTin theCNSmaylead toimplementationofbetterdeliriumprevention strategies.EPOhasan established safetyrecord,including usein newborn children. In ouropinion,the abilityofnonerythropoieticvariantsofEPOtoreversethetoxiceffectsofglutamatein theECS renders them optimalcandidatesfordeliriumtherapy.

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