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MAST CELL AUTOCRINICITY NEAR CEREBRAL ARTERIAL WALL "REVERSE GLYMPHATIC FLOW" AS PRIME TARGET OF ELECTROMAGNETIC EFFECTS

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SUMMARY

Efforts to disclose the mechanisms of transcranial therapeutic electro-magnetic fields (EMF) acting on the brain's cells (Marino, Kibleur) and recently immune cells (Gülöksüz) meet unsolved physiological details of blood vessels, exclusively arterial vasomotion or the non-glial-related former g(lia)-lymphatic flow (Iliff; Liu DX) - now replaced by an astrocytic AQP4-pipeline cooling the brain (Nakada 2014). Here within the convergent dyn4TAM-framework, which had suggested the first mast cell behavioral experiment (Fitzpatrick & Morrow 2017), three intertwined physiological concepts are contributed: A) "autocrinicity" – how flushed, thus absent, autocrine signals integrate external fluidics into cellular computations e.g. on motility: EMFs could increase such absences by targeting e.g. dipole-cytokines; B) a new concept of the arterial wall based on a tangible interpretation of the coronal histology of all arteries as a co-axial pulse-dampening engine (Treviranus 2012). In the brain this engine might provide the quickest cerebral outflow via the Cerebral IntraMUral Reverse Arterial Flow (Treviranus 2018b), while transmitting further forces acting upstream to the paravascular spaces; C) some key roles for mast cells in neuro-psychiatry (Silver & Curley 2013) and their interactive lymphatic and non-luminal vascular routes to the brain dictated by peripheral imprinting as to destiny (Csaba 1987) and destination (Treviranus 2013). Within the skull they might advance against para-arterial upstream currents.

Some known causal mediators of the effects of transcranially applied EFMs and puzzling results are then put tentatively in perspective with the above "tangible" models, e.g. by aligning probable induced currents with arterial segments or the new direct meningeal-calvario-myeloid channels.

Results: The case for a role of mast cells and diverse flows in transcranial electromagnetic brain therapy seems promising.

Key words: *transcranial electromagnetic stimulation - mast cells - arterial wall - vasomotion - autocrine signaling*

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INTRODUCTION

Those attained by a unipolar major depression episode (MDD) as adolescents face a nearly 20% risk to fail treatments and remain in MDD for half their lifetime constituting 1% of the population (Zorumski 2015). As far as response and short-term effects are concerned, repetitive transcranial magnetic stimulation (rTMS) especially with H1-coils (Gellersen & Kedzior 2019) have become non inferior to tACS (Leggett 2015). Depressions respond twice as well to alternating-current electro-convulsion (tACS) as to conservative therapies. Electro-magnetic field (EMF)-effects on the brain achieved by chemical and meanwhile non-convulsive therapies (Zuo 2018, Akbarnejad 2018, Gazdag & Ungvari 2019) reveal their immune (Pozzi 2018) and occasionally harming mechanisms slowly (Marino 2016, Singh & Kar 2017, Kibleur & David 2018).

Here hypotheses add topics this speculative field: 1.) autocrinicity as integration of external fluidics through flushed and thus absent signals into cellular decisions e.g. in motility: EMFs could increases such absences by targeting e.g. dipole-cytokines; 2.) non-canonical migratory routes of mast cells MCs to the brain (Pavlov 2018); 3.) contradictory (Springer 2017) key roles for MCs in psychiatry. These are generated from the convergent dyn4TAM-framework, which already suggested the first behavioral MC experiment (see Treviranus 2018a, pp. S 621-2; Fitzpatrick & Morrow 2017) stopping rodent sign-tracking by interfering with thalamic MCs within the first cortico-thalamo-subcortico-cortical circuit (CSTC).

The decreased excitability after continuous trains at 5Hz (Huang 2017) maybe reflects MC exhaustion. A likely site of relevant encounters between transcranial EMFs and the above putative processes include the "para"- arterial Virchow-Robin Spaces (VRSs), where MCs possibly advance counter-current along the adventitia (as granulocytes do intraluminally; Lyck & Engelhardt 2012), while this arterial VRS could be modulated by the parallel but mostly disconnected and acellular arterial intramural flow (related to pulse dampening). Through markers this astonishing intramural route showed up as the (hence also electrically) quickest "lymphatic" exit from the brain (Bradbury & Cserr 1974-84, Carare 2008). Here (3.2) it is explained via its biomechanics as read from histology (CIMURAF; Treviranus 2018b), whereby its reverse vasomotion against pulses could also induce a reverse flow in VRSs.

Electrohydrodynamics, vectorial alignment, and "ecological autocrinicity"

Only matter, electrons, but also ions or molecules function as charge carriers. "Drift velocity" becomes the product of obstructed mobility and EMF (Grimnes &

Martinsen 2014). Electro-kinetics require supercomputing (Götz 2010), but the low velocity of solute simply adds to the carriers' drift velocity. The EMF-generated brain currents between two electrodes between alternative paths thus pass in proportion to their conductances: notably along arteries' and vein's VRSs and along the said reverse intramural flow.

Electromagnetic therapy and its puzzling effects of frequency and alignment

In early studies applying rTMS scores of major depression (MDD) and perfusion varied with personalized frequencies at 20 or 1 Hz (Speer 2000): With 20 Hz applied at the dorsolateral prefrontal cortex (dlPFC) key affective centers and cortical areas (compatible with the medial three CSTCs) received more blood and the subgenual anterior cingulate cortex (sgACC; where MDD concentrates neuronal loss, Meier 2016), received less. Applied close to cortex rTMS induced distant therapeutic changes involving the sgACC and the default mode network, while surprisingly the executive control network (ECN) remained spared (Philip at al 2018). Through an occipital to left fronto-parietal long-range effect tACS too changed the correlation between such networks (Cabral-Calderin 2016), while antagonistically resonating with local slow (possibly vasomotive) fluctuations. The incisive accelerated ITB-rTMS rapidly showed improved integration with remote modules and cognitive parcing by complexity (Caeyenbergs 2019): maybe through thalamic cortico-cortical facilitation (Collins 2018).

ELECTROMAGNETIC NEUROPSYCHIATRY WORKS - BUT HOW?

Convulsive tACS and alternatives interactively change neurogenesis, angiogenesis, the glia, the hypothalamic-pituitary-adrenal (HPA) axis, and neurotrophic factor levels (Rotheneichner 2014).

Between analogies and fluctuations

Through rTMS the dlPFC seems to rebalance lasting "homeostatic plasticity" (Turrigiano 2007, 2017). High activity potentiates positive (LTP), low activity negative synaptic learning (LTD) through unsupervised feedback via presynaptic and postsynaptic molecules like tumor necrosis factor α (TNF-α) Under rTMS "low-frequency leads to LTD, high-frequency elicits LTP (≥20 Hz)" while it also stimulates innumerable underlying 1st and 2nd order causes. Direct current stimulation (tDCS) instead paused for around 10 minutes, results in motor-effects opposing those of a previous priming in sense, while neurophysiological effects hardly survive one hour (Karabanov 2015). On the chemical side rTMS close to the dlPFC increased its γ-aminobutyric acid (Levitt 2019). Such processes could as well be compensatory for a subcortical (Zuo 2019) cortico-cortical (Collins 2018) disturbances. While the hippocampi (HC) enlarge, favoring plasticity by tACS, it remains obscure despite modeling (Dokos 2013), how this comes about (Oltedal 2017, 2018) - even in peripheral nerves (Wang 2018).

Alternative tDCS (Dedoncker 2016) and rTMS (Serafini 2015) approach the efficacy of cumbersome convulsive tACS. The innovative "variable phase" tACS eliciting phased and traveling effects (Alekseichuk 2019) manipulates "resonances", reflecting statistically measured correlations which are actually blind to dimensionalities from e.g. CSTCs (Treviranus 2018a), in which tissue flows acquire weight, as reflected by signals of diffuse tensor imaging (MRT-DTI; Matsumae 2017, Sepehrband 2019, Dokos 2013) (Table 1).

Ecological autocrinicity

Only a few results (Silletti 1998, Doganer 2016) support a concept (beyond sensitivity to shear), that cells would be advantaged by autocrine signals flushed away by ecologically patterned and thus meaningful changes in external fluidics. Such an e.g. asymmetrical pattern of absences of signals (Lemmon 2016) would be integrated into cellular cybernetics and hereby e. g. modulate movement. A candidate molecule is adrenomedullin effecting motility (Zudaire 2006) and MC-degranulation (Lv 2018).

Induced EMFs conceivingly could remove autocrine signals from the uniquely immature and long-lived MCs while these travel (putatively) along cerebral arteries to where they mature and settle. While they guard the blood-brain-barrier (BBB) as key drivers of immunology, the intrusion of deviant MCs into the brain (where they activate macrophages which only once migrate to the brain (Ginhoux 2010)) makes them an important therapeutic target (Silver & Curley 2013, Treviranus 2018a). Extracellular microvesicles (György 2011) may soon qualify as the most interesting of such autocrine signals (Chen 2017).

PERIARTERIAL AND CEREBRAL INTRAMURAL FLOW AND VASOMOTION

The glymphatic enthusiasm revised

Interest in the interstitial fluid (ISF), which takes a 20-100% larger part of brain´s water than blood or CSF led to the "glymphatic" theory (Iliff 2012) which erroneously conceived a flush of the parenchyma by water drawn in by AQP4-channels from the «para»-vascular Virchow-Robin-Spaces (VRSs) expelling the parenchyma's ISF via venous VRSs back to CFS and as deep cervical lymph (Wang & Casley-Smith 1989). This "g(lia)-lymphatic" account was recently corrected by an inverse one, whereby astrocytes (ACs) provide a pipeline which circumvents the sealed BBB and no Starling-mechanism builds up (Hladky & Barand 2016). Few issues remain: a) the direction of flows (Bakker 2019) in the VRSs; b) the energetic origin of pressure gradients; c) the role of pressure pulsations; and d) the now contradicted (Nakada & Kwee 2019) contribution of the water-selective channels

Table 1. Putative Mechanisms of Transcranial Electro-Magnetic Therapies

Theory	Mechanism	R, G	Ref.
"BCM"	Post-/Pre-Synaptic learning		Cooper 2012
BCM in rTMS etc.	Analogy		Karabanov 2015
Fluid PNEI (tACS)	TRP-KYN, TDO/IDO	R	Gülöksüz 2015
PICs like TNF-α	↓ serum	R	Joshi 2016
P/AIC TNF-β, IL-5	↓ serum	R	Rotter 2013
Serotonin 5-HT	↓? binding to 5HT2AR		Yatham 2010
BDNF serum	↑ plasma	R	Polyakova 2015
VEGF serum	↑, mTOR Elfving 2012		Minelli 2014
HC cell proliferation:			
↗ →↘↘ (rat)	-		Nakamura 2013
((↑)) adult human / primates	*Natural development*	-	Sorrells 2018
↑→↗ rat	*Antidepressant drug, 0 ECS*	+A	Malberg 2000
*Neural Stem Cell (SGZ)		(-)A	Segi-Nishida 2008
*Neural Progenitor Cell	+/- NStC & ↑ NPG		Encinas 2006
Mossy fiber sprouting	↑ *(less, if ketamine)*		Chen 2001
DA to Mossy fiber	↑		Kobayashi 2017
Human HC volume	↑	R	Oltedal 2018, *Powell 2017*
Human DG volume	↑	R	Nuninga 2019 s
HC volume	*No ECT, Escitalopram*	*R G*	*Powell 2017*
HC, AMYvolume	↑	R	Tendolkar 2013
HC, AMYvolume	↑	R	Nordanskog 2103
Insula volume	↑	R	Van Eijndhoven 2016
Any neurogenesis ECS	↑	R	Alemu 2019
HC R ant. Perfusion	↑	R	Leaver 2019
dmTHAL	↑ ? *CSTC*	R	Leaver 2019
Glucose uptake	↓ PFC		Henry 2001
Spontan-fluctuation	*CIMURAF ?*		Cabral-Calderin 2016
Vasomotion	*CIMURAF ?*		*This project*
Autocrinicity			*This project*
Mast cells			*This project*
MC disorders			Georgin-Lavialle 2016

In Italics: Sources referring to Antidepressant drugs or Hypotheses followed by the author (e.g. Cerebral Intra MURal Flow).
Abbreviations: CSTC: Cortico-subcortico-thalamo-cortical circuit; PIC pro-inflammatory cytokine; TRP-KYN, TDO/IDO: Tryptophan-Kynurenine metabolism through TDO-/IDO-enzymes; mTOR: mechanistic Target of Rapamycin; dmTHAL: dorsomedial thalamus; ECT: Electro-Convulsive Therapy; TNF-α: tumor necrosis factor α R: clinical response; G: genetical evidence; 0/(-) A: chemical Antidepressants for comparison (Italics): No or negative effect

(aquaporin-4; AQP4), since these are expressed inside the BBB and not dedicated to water exchanges with the outside. Astrocytes (ACs) use AQP-4 at the podocytes to acquire H20 from just above the cortex (Suzuki 2017) for the AC's own hydration and again to expel H20 into the VRS. During heat-alarm the latter shut down to hydrate ACs (Nakada 2014). There is no lymphatic "flush" like in other tissues.

Wondersome intra- and extramural "peri"-arterial flows

Following the clearance of Abeta (Carare 2008, Okamoto 2012, Ball 2010), from also cortical interstitial brain fluid (Bakker 2016), a wondersome rapid and reverse marginal "peri"-vascular intramural route had shown up in rodents (H.F. Cserr 1974-1984; Szentistvanyi 1984). An application of peripheral arterial reflected pulse waves to this process (Schley 2006, Diem 2016, 2017) lacked the required reflection surfaces (Coloma 2019) and valve-like macro-nano-links.

The Cerebral IntraMUral Reverse Arterial Flow-model (CIMURAF; Treviranus 2018b) was derived from a previous Co-axial Arterial Wall Engine (CAWE) interpretation of the aortic wall, proposed originally (Treviranus 2012) to explain its exceptional biomechanical resistive persistence.

The Co-axial Aortic-Wall-Engine: a smart macro-engine?

The CAWE-model is readily verified by coronal histology, but requires scientific testing. Since at least molluscs' arterial vascular smooth muscle cells (VSMCs) do not (usually) "hold hands", but in the tunica media attach obliquely to co-axial tubes made of elastic laminas

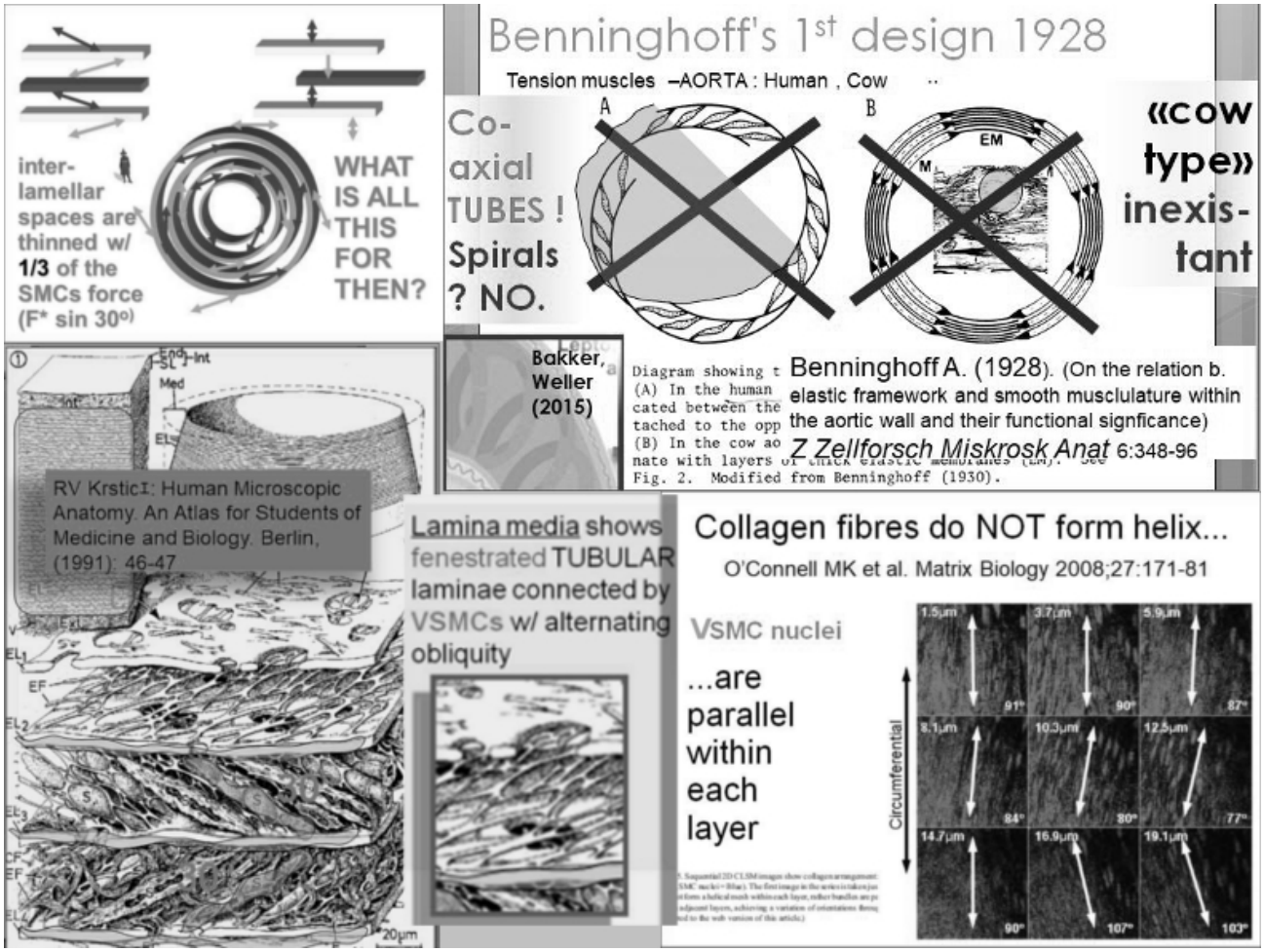

Figure 1. How arteries were seen: The two blueprints of the textbook author anatomist A. Benninghoff (1928) were both wrong. The helical version accepted by Bakker (2015) was refuted by O'Connell (2008). The correct blue-print by R.V. Krstic (1991) went unnoticed. The first insert shows the Co-Axial-Wall-Engine-model (Treviranus 2012)

starting with the lamina interna (López-Guimet 2017), which are separated by pressurized watery inter-lamellar compartments (ILCs; Carew 1968, Davis 1993). The human aorta is made out of more than 60 of such tubes stuck inside one another. Also, the sense of this obliquity alternates radially from tube to tube. Hereby most (~3/4) of the VSMCs more tangential action does not result in pressurizing by radial contraction (~1/4), but in small co-axial rotations (<10°) of the tubes, which in the aorta e.g. possibly follow the heart rate, but elsewhere might be related to the several-fold slower «vasomotion» (see below). These torsional movements, induced by VSMC contraction, extend anti-parallel elastin fibers, which after relaxation restore the system to baseline, whereby a simple harmonic oscillator is built. This neglected co-axial cylinder blueprint of arteries (Hayman 2016) is more hidden in other arteries (Hill 2016, Hinderer 2015, Eoh 2017) (Figure 1).

At the same time such neurally induced segment by its alternating axial momenta at each ILC - like a «christmas cracker» - causes two slight hyperboloid circular embayments (HCEs). When such a segment moves upstream to dampen the pulse (by appropriate nervous instigation-relaxation of the VSCMs) coupled HCEs will resolve and renew themselves over a traveling distance. This will drive a "multilayered cushion" with a bow wave and a stern suctioning end. Within every ILC a) incoming contrary arterial pulses from heart-like pumps are dampened by working against the VSMCs´ torque (the primary evolutionary scope) and b) water is drawn into the ILCs of the segment – the fenestrations becoming radially aligned by torsion in order to refill them, and c) CIMURAF is accelerated in its reverse upstream direction behind the stern HCE, the radial outflow being shut again. This is peculiar to the brain where the radial lamellar fenestrations are twice as numerous, albeit obstructed by myo-endothelial-cell protrusions (Sandow 2009). CIMURAF is steered by four vasomotive nerve systems (Ainslie 2014, Taktakishvili 2010, Roloff 2016), and stronger during sleep (Xie 2013) (Figure 2).

Heat and not self-erasing impacts of electromagnetic fields on arteries

Although arteries, being larger and less complex per volume, can be expected to be «more aligned» to the curved and changing EMFs, the problem of complex and

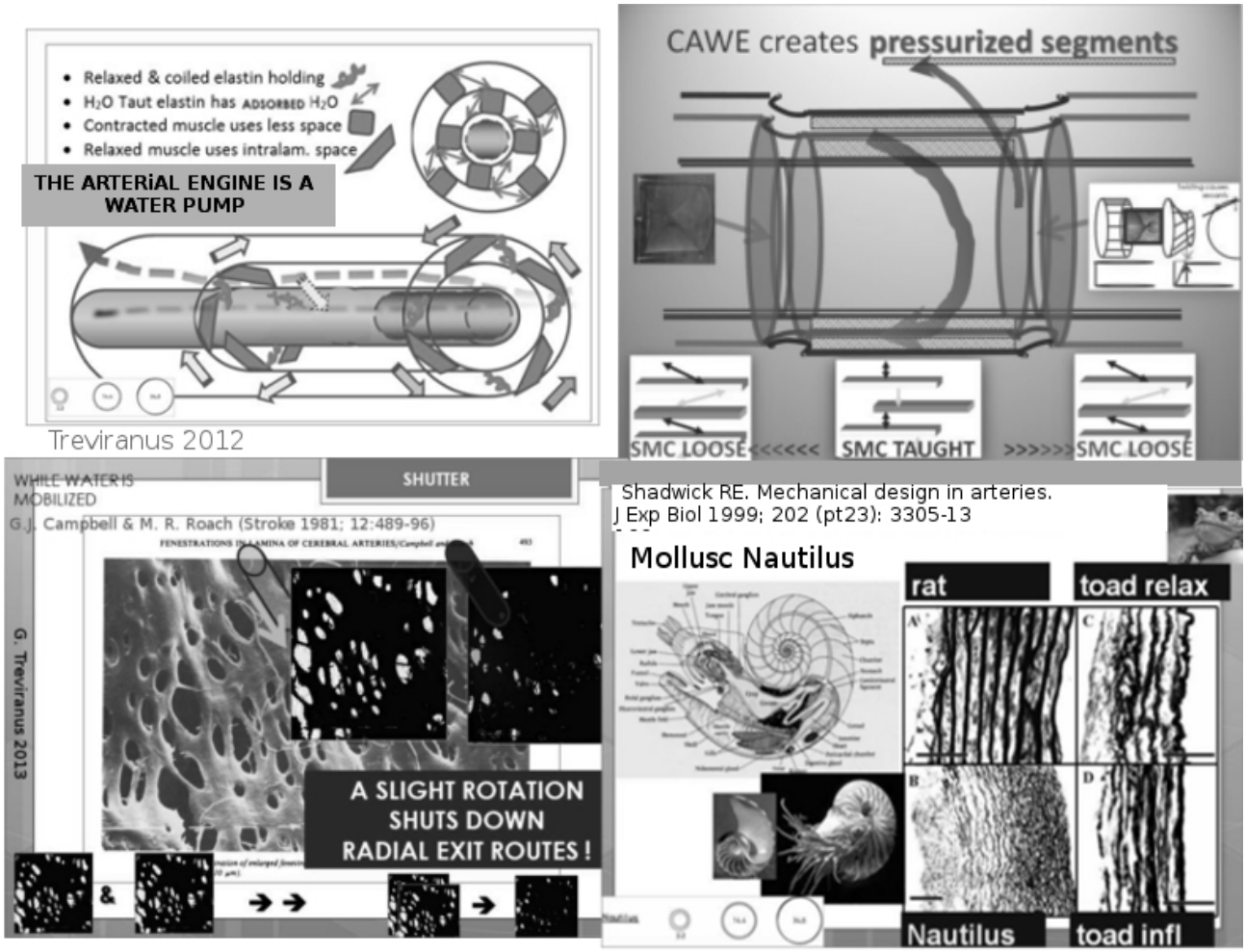

Figure 2. The Co-Axial-Wall-Engine-model with two interlaminar spaces with Vascular Smooth Muscle Cells axially twisting three laminar tubes against each other in a leftward vs. rightward sense creating a sliding pressured chamber between two zones between hyperbolic embayments. The shutter-mechanism effectively shuts down the radial tortuous exit towards the VRS as shown by sliding two overlaid copies of fenestrated laminae (image from Campbell & Roach 1981). Mollusc, reptile and mammals all show the exact same aortic blueprint (Gosline & Shadwick 1982)

opposite self-erasing effects of EMFs persists (see *Between analogies and fluctuations*). The effects of alignment followed during biphasic stimulation of cortical interneurons (Wang 2018, Sommer 2018) hardly reflect the tissue's neuronal, axonal or subcellular intricacies.

EFMs probably also pass through ionic gap junctions connecting same and different mural cells. But muscle contractions nevertheless require neuromuscular junctions (Kean 1974, La 2019, Kotecha & Neild 1988) - apart from vague nano-electro-sensitivity (Suzuki 2017, Oosawa 2018).

The VSMCs providing CIMURAF therefore are only allowed to perform the coronal obliquely tangential contractions following the CAWE-engine's architecture. How EFMs from diverse angles will affect VSMC-contractions remains understudied.

After the substitution of the "glymphatic" paradigm (see *The glymphatic enthusiasm revised*) the degree to which ACs might react towards heating (Nakada 2014) by the EMF-waves might move center-stage since 5/6 of brain's perfusion remains unexplained. MCs have at least one highly temperature-sensitive proton channel (Kuno 1979), which is very present in microglia and stroke (Wu 2012). Both K+-channels KCC2 and NKCC, determining inhibitory transmission MDD or epilepsy via intracellular Cl- , decrease the latter in proportion to temperature (Hartmann & Nothwang 2011). About brains' temperature physiology despite clinical questions little exists (Wang 2014): The BBB becomes highly permeable upon heating up to fever and just beyond neurons perish. Axons instead concentrate the heat generation capacities with a role in neurotransmission.

Intramural muscles drive the para-vascular flow in Virchow-Robin spaces

The VRSs remained puzzling since their first description (His & Bastian 1867). Today their waste-flushing function (Di Marco 2015) stays crucial and pluri-segmental MRI 4D-velocimetry shows its deterioration along the Alzheimer spectrum (Rivera-Rivera 2016).

CIMURAF-engine and reverse acceleration in the Virchow-Robin-Spaces

Since the lamina interna is water-tight and the twisting dynamic of the wall opens the shutters in the segment right behind the bow wave, while the stern suction accelerates the CIMURAF within the normally radially closed ILCs, a compensatory similarly counter-current flow is predicted for the VRS. When the segment travels upstream the opportunities for radial influx first shortly increase by the initial segment up to compensation, but then subsides (while behind the stern HCE of the ILCs the radial exits are again obstructed). Thus there is always more radial influx into the wall upstream than downstream and this gradient is reinforced by the traveling speed of the segment, while the VSMCs keep working against the cardiac muscle in order to dampen the destabilizing effects of the pulse on the wall and the tissue homeostasis. This account is reversed if one assumes that the shutters would close in the segments, but that would destabilize the wall over the relaxed parts.

CSF-tracers are enriched up to 40-fold in the circle of Willis, (Bradbury 1981) which in fact cannot have sliding torsional segments and therefore could testify for the capacity of CIMURAF.

Vasomotion

The CAWE-blueprint concerning all arteries could be related to the slower vasomotion (VM) - for which only approximative molecular processes are put forward (Cole 2019). VM denotes rhythmic oscillations of about 10/min in the diameter of even isolated arteries and arterioles, which – in a way maybe related the origin of the BOLD-signal of MRT – seem to be neuronally entrained by energetic needs of cortical neuronal activities (Mateo 2017). VM, as CAWE/CIMURAF, seems to be unique for arteries. The wall of veins do not show this blueprint, and only games of nature like the original bat wing (Wharton 1852) show entirely different oscillations (Liu 2014, Scholbach 2016, Arpi 2018). Thus a "review" (Van Helden & Imtiaz 2019) focussed entirely on lymphatics.

VM can be influenced by many factors and correlates with cycling of force-generating myosin cross-bridges in VSMCs and their molecular and membrane potential context. The ensuing «flowmotion» reflects environmental physical and local influences from VSMC, paracrine ECs, perivascular fat (Nava & Llorens 2016), and from other cells. Where nitric oxide (NO) is low and availability and sensitivity to thromboxane (TBX) are high TBX elicits strong VM (Horváth et al. 2010). MCs again can be strong producers of TBX (Macchia et al. 1995).

IMPRINTABLE MAST CELLS: UNDERRATED AND MIGHTY

One-cell organisms can be induced by a single imprinting signal to respond lastingly in another way. György Csaba extended this pioneering research with early glandular hormones to similarly imprintable MCs (Csaba 1987, 2012, 2014). MC are complex hubs (Niarakis 2014). They guard interfaces of tissues, varying their complexity. They respond to over 200 often combinatorial chemical, often psycho-social, neural, or physical, i.e. receptor- or surface-mechanical, hot-cold-, and electrical and/or fluidic inputs. These may doubly imprint them as to a) their migratory destination in the CNS through selective molecular pairing between cell and paths still immature cells, and b) as to their mature persistent destiny. Following signal integrations MCs respond through a dozen release modes. Rat peritoneal MCs e.g. one hour after injection were close to thalamic blood vessels, among 90% previous residents, and deep to the basal lamina, in nests of glial processes (Silverman 2000). MCs "orchestrate" fellow immunocytes early in response; but they can survive for years as guardians of barriers and homeostasis (Table 2).

The mast cell - "lymphatic cauldron" relations

Only recently meningeal lymphatics were discovered (Aspelund 2015, Louveau 2015, Absinta 2017) and channels draining from the calvarial bone-marrow (Cai 2019): a highly promising route for e. g. MCs to cause insomnia, hallucinations or hidden lesions in the cortex.

As, often subverted, first-line defendants and later "orchestrators" of innate and adaptive response and as likely intestinal lipid uptake monitors, MCs join the well-isolated inflammatory cauldron of the collecting and thoracic lymphatics to orchestrate immune responses in lymphatic tissue and to evaluate metabolic or toxic signals. The lymphatic ECs in fact decisively interact with MCs - else obesity occurs (Pal 2017, Gasheva 2019). Furthermore the lymphatics are regulated by autonomic peptidergic nerve signals (Ito 1989), which are often involved in permeability and MC communication.

Hypothetical events between lymphatics and mast cell

After distal challenges the, passive, lymphatic transport could be hastened by a plausible proximal neurally induced "sieving" of obstructing fluid (sigma-1-receptor; Trujillo 2017).

«IRF-4-dependent CD11b-+ dendritic cells» (DCs) control the permeability of lymphatic collecting vessel (Ivanov 2016) through NF-κB signaling (Grumont & Gerondakis 2000) to their CCR7-receptors (already calling them into initial lymphatics; Pflicke & Sixt 2009), and later become "embraced" by the vascular ECs (Teijiera 2013). Now the NF-κB stems from a predominant MC/histamine/NF-κB axis (Nizamutdinova 2016), shielding the lymphatic's transport and barrier functions (Kang 2009), unless by failure the perivascular tissue becomes inflamed or infected (Zolla 2015).

Table 2. Incomplete synopsis of mast cell concepts. Mast cells are very versatile and their faculties seem to serve various "scopes" of which the "mechanisms" and "main proofs" are referred to leading sources

Theory of scope	Mechanism	Main proof	Source
Bioeconomical	Complexity deciding	0.5 bio years old	*This project*
Immunometabolism	(Fat sensing)	Masted by lymph	Paul Ehrlich 1877
Morphogenesis			Crivellato & Ribatti 2016
Early host defence	Etosis	Only armed cell	Möllerherm 2016
Adaptive Immunity	Lymph	Pellets with PICs	S. N. Abraham 2009
Guardians of BBB	PNEI		T. Theoharides 1996
Mind modulators	Ethology	Molecular biology	Silver & Silvermann 1996
Meningeal		Migraine	V. Dimitriadou 1997
Gut-Brain-Axis		AutismMoura	T. Theoharides 2015
Neuropsychiatry	BDNF (+)	Mastocytosis etc.	Moura 2011, Afrin 2015
Oligodendrocyte	*Tryptase*	*Complement 4 ?*	Medic 2010
CSTC modulator	Cognition	Sign-tracking (rats)	Fitzpatrick & Morrow 2017
	MC degranulation	*Uncertainty Orient*	*Treviranus 2018a*
Imprintability:		Destiny	G. Csaba 1987
Imprintability		*Destination Author GRS Treviranus*	*This project*
Transgranulation			M. Wilhelm 2005
Epigenetic changes	Histone	Tryptase	F. Levi-Schaffer 2014

In Italics: Sources referring to Hypotheses followed by the author

Exploring non-canonical migratory routes the following sequence can be imagined after "sieving" (Treviranus 2013): (A) Since MCs in order to activate lymph nodes (Kunder 2009) produce cytokine-protecting-pellets (CPPs, my term) which shield pro-inflammatory cytokines (PICs) from ultra-rapid disposal - such CPPs carrying TNF-α (which is also a chemokine) can be expected to be (B) spilled out of the lymphatics and (C) to attract MCs to where they happen to go. Then (D), occasionally a space would be created by the MC adjacent to a vessel and filled with CPPs, again through TNF-α, (E) tight-junctions (TJs) could be cracked (Marcos-Ramiro 2014), opening (F) a path into the main lumen or into a VV. Thereby (G) being rolled in and dragged on by laminar flow CPPs could advance. When (H) stuck inside a VV the CPPs – restarting the rope trick – would attract MCs or crack the TJs. At lympho-arterial crossings (I) MCs could switch vessels (J): a.) Towards the anterior cerebral circulation: lymphatic duct to aortic arch from below into the carotid "chimney" modulating the carotid, the jugular vein, and the vagal nerve; b.) Towards the posterior circulation: from the lymphatic retro-clavicular "end-curve" of the duct to the vertebral artery - MCs could thereby (J) cross-over from the lymphatics into the lumen or into a VV within arterial walls. Similar processes actually contribute to vascular pathologies e.g. in hepatic veins (Yamamoto 2000, Takahashi-Iwanaga 1990, Lukacs-Kornek 2016). Adventitial MCs have been described for long in relation to vasospasm, dissection (Wågsäter et al. 2016), and atherosclerosis (Lindstedt et al. 1999) as well as their relation to neurogenic inflammation (Laine et al. 2000) in blood vessels, and lymphatics (Pal 2017).

At the skull's border, where the acellular intramural CIMURAF (Treviranus 2018b) leaves the arterial wall for the ethmoïds, (K) MCs could surface on the adventitia and enter the VRS, advancing counter-current. The ensuing fluidic information together with chemokines and apt (imprintable) pairings of the EC surface molecules with their own, could (L) steer them into specific brain areas. Such hands-on details on migratory paths are being sought (Martinelli 2014).

Mast cells as related to electromagnetic therapies

MC regulate many cerebral sites, but, besides their strong presence in the stress systems, their main neuropsychiatric influences stem from their meningeal or thalamic residency. Currents applied to rodents have terminated thalamo-cortical spikes and waves, and provided on-demand anti-epileptic activity for weeks (Kozák & Berényi 2017). Also do MCs produce and store dopamine (Rönnberg 2012). Some dysfunctions in Parkinson's diseases refer to the thalamus: e. g. tremor to insufficient self-inhibition of the ventral intermediate thalamus via external dopamine (Caligiore 2019, Dirkx 2017). Motor performances improved through rTMS reduced the jointly pathogenic serum IFNγ and IL-17A, produced by striatal Th1- and Th17-cells (Idova 2012).

Grey matter cortical changes in MDD (Harrison et al. 2006) or schizophrenia (Xu 2017) instead are either due to isolated deficits in function (ACC, lPFC, putamen) or structure (frontal and temporal cortex) or in both (ACC, insula), whereby thalamic MCs could destabilize function (and neurotrophic activity) at the

CSTCs, and meningeal MCs could functionally disturb or attack neurons and oligodendrocytes directly after intruding e. g. from arterial walls of the anterior arterial supply, which densely crosses the insulas.

CONCLUSION

The challenge to explain the most effective treatment for several neuropsychiatric conditions should profit from incorporating not only "fluid" Psycho-neuro-endocrino-immunology, but also the highly versatile, long-lived, and mighty mast cells ascending to destinations and destinies within the brain from the lymphatics and via other non-canonical routes, possibly co-regulated by negative "autocrinicity". While the blueprint of arteries by itself calls for a comprehensive investigation it contributes to understand the regulation of intracerebral flows. All these are candidates as targets of electro-magnetic fields induced in the brain for therapeutic purposes.

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