

Review

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Review

Growth, Aging and (Epi)Genetics in Light of Piezo2 and Quantum (Gravity) Theory

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Abstract

The current manuscript is meant to introduce how piezo2 channelopathy may play a critical role in (epi)genetics, when it comes to development, growth and aging initiation from a neurocentric view. Accordingly, it demonstrates how the principality of excitatory Piezo2 ion channel may not only reflected in Piezo cross-frequency coupling, transcription activation, ultradian event sensing and modulation, but might also fine-modulates emergent entropic force from gravity and (epi)genetics, hence underscoring its principality not only in proprioception. The implicated Piezo ion channels, especially Piezo2, have cellular, inter-cellular, compartmental and systemic effect through a Piezo system, however the underlying backbone ultrafast (glutamatergic proprioceptive Piezo2) system may carry the principality. Syndecans as co-functioning accessory ligand of Piezo2 may serve the non-linear dynamics of the ultrafast non-linear time-delay system in order to quantum tunnel/synchronize protons in an ultrafast fashion into the suggested anticipatory coupled hippocampal chaotic system. The co-function of the intrinsically disordered intracellular domain of Piezo2 and the intrinsically disordered ectodomain of syndecans may posit the critical structure in this proposed ultrafast non-linear dynamics that may be impaired due to Piezo2 channelopathy, leading to altered response to postural perturbations, consequently might cause an increased the risk of non-contact injuries. Proton affinity switch on proprioceptive glutamatergic terminals may not only induce acquired Piezo2 channelopathy and resultant switch to glutamate-based signaling, but may miswire protons as well through the lipoxygenase pathway. This proton miswiring may also inhibit fine-regulation of excitatory AMPA information processing in neuronal synapsis. After all, acquired Piezo2 channelopathy may posit such an initiating critical primary damage that impacts development, growth and aging through (epi)genetics, however quantum (gravity) theory is needed for translation.

Keywords: Piezo2 channelopathy; ultrafast system; growth; non-linear dynamics; epigenetics; gravity; quantum theory

Introduction

The current manuscript is meant to introduce the (epi)genetics at play in relation to Piezo2 ion channel, when it comes to growth and aging initiation from a neurocentric view, mainly demonstrated through delayed-onset muscles soreness (DOMS) and amyotrophic lateral sclerosis (ALS), but traumatic brain injury (TBI) and especially Angelman syndrome (AS) is used for mechanistic presentation as well. Correspondingly, the pathophysiology onset of DOMS and ALS is theorized[1] to be initiated by an acquired functional microdamage of Piezo2 at the terminals of the oscillatory glutamatergic Type Ia proprioceptive fibers within the muscle spindle[2]. This acquired Piezo2 channelopathy is also coined as the primary damage, or the one common root cause of aging

onset[2], in line with the primary damage aging theory[3]. Indeed, an ALS-based genome-like association study (GWAS) revealed the importance of these type of glutamatergic fibers on which cell-autonomous neuron-specific processes may prevail on route to neurodegeneration[4]. Moreover, the same GWAS suggested the casual role of high cholesterol level, perturbations in vesicle-mediated transport and autophagy[4]. Other ALS-related genetic works highlight the oligogenic background of the genetic disorder of ALS, while rather excluding the casual role of mitochondrial dysfunction and implying it as a consequence[5]. All these mechanisms revealed by ALS-related genetic analyses are proposed to be at play in DOMS gateway to pathophysiology and that is acquired Piezo2 channelopathy on intrafusal Type Ia glutamatergic terminals[2,6].

The cholesterol level decreases as a result of repeated eccentric exercise[7], that leads to DOMS, but this is in contrast to the implicated casual high cholesterol level in ALS[4]. Moreover, the suggested transient neural switch due to Piezo2 channelopathy at Type Ia glutamatergic terminals of DOMS[8] leads to impaired proprioception[8], increased insulin resistance[7], decreased energy generation[9], delayed pain sensation[8]. These symptoms are the cardinal hallmarks of the challenge of aging as well, however the DOMS-induced lower cholesterol stands out in an opposing way to aging and ALS pathomechanism. Noteworthy that the decreased cholesterol level as a consequence of DOMS is devoted to elevated excitatory proprioceptive Piezo2 function since it depletes membrane cholesterol and negatively charged lipids in its vicinity[10]. Let's consider when eccentric, or forced lengthening contractions, are sustained for two weeks without regeneration periodization[11]. As a result, the mechanical threshold decreased from the second day continuously up to the ninth day (off note this is exactly the time window of DOMS associated pain), both regenerating and necrotic muscle cells were decreased, nerve growth (NGF) expression significantly increased, taut bands were palpable from the third day to the eighth day as an indication of myofascial pain[11]. Earlier it was implicated that DOMS may represent the revival of a growth-like reflex[8], while the current author proposes that the 9 days lasting pain-related time-window due to continuous eccentric loading without regeneration reveals growth and pain extinction thereafter and degeneration is at play from there on. These mechanisms are the two ends of a spectrum, and repeated bout effect (RBE) of DOMS may explain the in between mechanism. When the initial bout of severe DOMS-inducing unaccustomed eccentric exercise is repeated then reduced DOMS symptoms are induced in at least 6 months after the initial DOMS effect, and this adaptation is lost only within 9 to 12 months[12]. However, the neurogenic theory of DOMS rather calls these of RBE time windows as memory dimensions of neural damage instead of muscle adaptation due to RBE effect[1,2]. Beyond memory, a fairly precise intrinsic clock is emerging in the background of DOMS and RBE that implies a 1-3 days of Piezo2 channelopathy (peak pain interval – Primary Damage Phase), 7-10 days of pain window (Secondary Injury Phase) that could extinct form memory in a year (peripheral neural damage related memory extinction in the absence of RBE). However, ganglionopathy evolves in the presence of sustained RBE and in the absence of memory extinction after a year (Tertiary Injury Phase) and further prolongation of Piezo2 channelopathy result in accelerated aging after 10 years with central nervous system involvement (Quadric Injury Phase), as the quad-phasic non-contact injury model suggest it[2]. Accordingly, the current author proposes that not only growth and pain depleted and dysregulated among other mechanisms, like neuroinflammation, the autonomic nervous system (ANS) and neuroimmune system, downstream of this non-contract aging model, but lipid metabolism as well as a consequence of chronic Piezo2 channelopathy. Accordingly, acute Piezo2 channelopathy depletes cholesterol, however longitudinally chronic Piezo2 channelopathy induced cholesterol depletion may instigate a compensatory feed-forward systemic cholesterol increase due to lipid metabolism dysregulation because cholesterol cannot be built in to membranes properly at the primary damage sites.

Piezo2-Initiated Non-Synaptic Neurotransmission

Eccentric contractions are anti-gravitational and it is theorized that time, spatial and speed encoding emergent from gravity are synchronized to the hippocampal theta rhythm in accordance

with the quantum (gravity) theory[13]. Not only an ultrafast Piezo2-initiated quantum tunneling of protons[14], but even a Piezo2-initiated wormhole is hypothesized between the Type Ia proprioceptive terminals of the muscle spindles and the hippocampus under allostatic stress[13]. Noteworthy that Piezo2 was shown to be the principle proprioceptive ion channel in mechanotransduction[15], however other ion channels also contribute to proprioception, but these contributions are suggested to be further downstream of a hierarchy[2,13,16]. Indeed, an ultrafast pain system is present[17], hence must be an underlying ultrafast system as well where its damage should be reflected in (ultrafast) pain. This fine regulation, the equivalent of ultrafast mechanotransduction, suggested to be initiated by Piezo2[2,13,16], regardless of the negation of PIEZO2 in the aforementioned ultrafast pain system study[17]. Only PIEZO2 was deleted and ASIC ion channels (as proton-gated channels), and Na_v ion channels were not affected in this study. For example, Piezo2 and ASIC2, $\text{Na}_v1.1$ co-signaling is indeed needed for proprioceptive signaling from the muscle spindle, but it is suggested that Piezo2 is the only one among them that could initiate the quantum tunneling of protons as the basis for the ultrafast long-distance non-synaptic neurotransmission[2], not to mention the inducement of wormholes as the backbone of brain axes, like the proprioceptive muscle-brain axis[13]. In support, a recent study demonstrates that only in the presence of PIEZO2 when rapidly adapting currents are activated in a very fast way[18], as was theorized earlier[2]. Hence, the current author proposes that actually the absence of Piezo2 function (deletion/functional microdamage/channelopathy) is needed in order to instigate ultrafast pain in the skin, or delayed pain sensation in the muscle spindle. Both of these pain sensations have principal evolutionary relevance, since the former one induces the protective withdrawal reflex, while the later one provides 6-8 hours of escape from danger without the limitation of pain, however later a growth-like reflex is revived, as the muscle 'gain' of DOMS shows.

Important to note that Piezo is evolutionarily highly conserved and it was theorized earlier that Piezo2 is the principle receptor for electromagnetic field induced oscillating energy [2] and blue-light detection [19]. Since it is demonstrated that PIEZO2 is the precise/fine mediator of magnetic stimulation[20] that indeed implicated Piezo2 as the fine/ultrafast sensor of magnetic field (MF). Moreover, this study also showed that magnetomechanical stimulation activated Piezo2 and reversed inhibition of neurite growth, hence improved autism-like behavior in mice[20]. Another study also showed that PIEZO regulates root growth in Arabidopsis in response to MF and blue light signaling[21]. It is also intriguing that PIEZO was essential in the leaves in order to transduce MF and blue-light towards the roots where PIEZO was upregulated[21]. This not only means that PIEZO has a principal role in growth, but long-distance mechanotransduction of MF and blue-light by PIEZO is revealed, as earlier theorized[2,13,19]. Accordingly, combined treatment with peripheral and transcranial electromagnetic stimulation made faster recovery from DOMS when symptoms were considered, not to mention improved velocity and sports performance of affected athletes[22]. Important to note that only peripheral electromagnetic stimulation (not combined with transcranial electromagnetic stimulation) did not show this curative effect on DOMS[23]. These studies clearly reveal the existence of Piezo2-initiated long-distance neurotransmission with a prime role in growth that could be stimulated and revived by (electro)magnetic stimulation.

In humans, coaches have long employed the "no pain, no gain" training strategy in order to instigate muscle gain by DOMS inducement. Since, acute stress response (ASR) is part of DOMS-inducement, therefore it is important to make a distinction between two stages of allostatic stress according the neurogenic theory of DOMS[2]. One is theorized to reflect intact and inactivated Piezo2 and that is the equivalent of good stress according to Selye's stress theory[2,13]. Noteworthy, that Type Ia proprioceptive neurons not only glutamatergic, but GABAergic as well, and GABA may inactivate Piezo2 and switches proprioceptive mechanotransduction to ASIC3 containing Type II proprioceptive fibers[24]. This stage of allostatic stress is homeostatic that implies fine regulation of remodeling, inducement of the inflammatory reflex and adaptation with intact ultrafast long-distance non-synaptic neurotransmission between Piezo2-Piezo2 (Piezo2 system), cross-frequency coupling between Piezo2-Piezo1 and Piezo1-Piezo1 (all together constructing the Piezo system)[2,13].

However, over-excessive proprioceptive mechanotransduction under allostatic stress may induce bad stress or Piezo2 channelopathy with impaired ultrafast long-distance non-synaptic neurotransmission between Piezo2-Piezo2, and impaired cross-frequency coupling between Piezo2-Piezo1 and Piezo1-Piezo1, and the inducement of the gateway reflex[2,13]. In addition, this primary damage not only breaches the limits of remodeling (wound inducement), but its chronic form may even miswire proprioception, dysregulate remodeling since wound healing is unfinished[2,13]. In support of this stress-related evolutionarily role, Piezo is indeed the ion channel that modulates mechanical stress even in the heart of *Drosophila* and the loss of function mutation of PIEZO stops this mechanical stress buffering, not to mention induces pathological remodeling[25]. Further in support of Piezo2's involvement in stress modulation, a recent TBI study detected the critical role of Piezo2 in the stress-related defensive arousal response (DAR)[26]. DAR is evoked by threat-induced visual and auditory inputs in the context of motor abilities[26]. Earlier papers not only find DAR analogous to ASR, but also proposed that DAR is mechanistically analogous to the ultrafast matching of the Piezo2-initiated eye-brain, auditory/vestibular-brain, and proprioceptive muscle-brain axes within the hippocampus[27,28]. The reintroduction of PIEZO2 in this TBI study promoted the decrease in the escape latency and increased escape speed during DAR[26]. Moreover, the functional loss of PIEZO2 induced increased escape latency in TBI[28] resembles to the findings of a DOMS-related study, namely eccentric exercise increased the M-wave latency and implicated reversible motoneuronal damage, not to mention ruled out muscle spindle origin[29]. However, later another DOMS-related study showed significantly increased medium latency response (MLR) of the stretch reflex due to DOMS effect[30]. In addition, the authors of the MLR study reasoned that the transiently impaired muscle spindle-derived proprioceptors due to Piezo2 channelopathy in DOMS may have resulted in VGLUT1 disconnection on motoneurons, hence the preceding increased MLR is to blame for the increased M-wave latency of motoneurons[8,10]

It has been long known that heat shock factor 1 (HSF1) not only pivotal to stress-derived expression of heat shock genes, but reversibly localizes to nuclear stress granules within seconds[31]. Important observation that repeated electromagnetic field stimulation positively impacts cellular senescence via HSF1 by slowing aging and cell death[32]. This effect is proposed to be delivered through proton tunneling due to repeated electromagnetic field stimulation as driven quantum oscillator of water[32] with likely important underlying concerted quasi-simultaneous proton hopping phenomenon along a H-bonded network of water molecules in line with the Grothuss-mechanism [33]. A similar driven quantum oscillator function was assigned to Piezo2 via VGLUT2 in support of the proposed ultrafast proton-based long-range non-synaptic oscillatory synchronizational neurotransmission from the muscle spindle to the hippocampus[2]. Indeed, Piezo2 was suggested, and confirmed[20], to sense electromagnetic field-induced oscillating energy[2]. Furthermore, Piezo2 channelopathy was proposed to activate non-coding heat shock RNA-1 on route to HSF1 activation[16]. Nevertheless, these stress-driven pathways are suggested to be impaired and lost due to irreversible Piezo2 channelopathy in ALS. Interestingly a recent genetic reanalysis of an ALS cohort detected pathogenic-leaning VUS splicing variant of HSF1 among ALS patients[16]. Finally, it is also remarkable that stress regulates hippocampal neurogenesis as well[34].

(Epi)Genetics in Light of Piezo2

The “special genetic signature” of Piezo2[35] has been long implicated and Piezo2 channelopathy is even hypothesized to be a principle transcription activator[36]. Even when Piezo2 channelopathy was proposed in the scientific literature first, the principality of proprioceptive terminal Piezo2 channelopathy was emphasized as the most “profound life-sustaining, genetically preprogrammed hardwiring could be affected by their proposed mechano-energetic microlesions, which could have relevance in DOMS, noncontact injuries, neurodegeneration, oncology, autoimmune diseases, pain management and sexual dysfunction.[10]” Moreover, it was also highlighted that “not letting these proprioceptive nerve terminals regenerate or return to their

preprogrammed functioning, as well as elongated loading of the secondary compensatory pathway, could have progressive consequences.[10]"

Noteworthy when it comes to DOMS neurocentric theory that in this principality of transcription activation it is implicit that the muscle stem cells are feed-forward activated by Piezo1 in response to the impaired Piezo2-Piezo1 cross-talk due to the proposed intrafusal glutamatergic proprioceptive terminal Piezo2 channelopathy[2]. This also means that under homeostatic conditions, muscle adaptation is fine-regulated by long-distance Piezo2-Piezo2 cross-talk (ultrafast backbone of muscle-brain axis) between the aforementioned intrafusal proprioceptive fiber terminals and hippocampal neurogenesis. This fine modulation is in contrast to DOMS where not only exaggerated contractions are induced as a consequence, but exaggerated stem cells activation and likely neurogenesis as well due to feed-forward Piezo1 activation as a result of impaired cross-frequency coupling of the Piezo system. Consequently, wound healing needs this feed-forward exaggerated mechanism in support of closure (hence revival of a growth-like reflex), however when Piezo2 channelopathy becomes chronic then the wound healing is unfinished in association with combined dysregulated and depletory mechanisms, stemming from the ongoing primary damage[2]. Notable that fibroblast are also activated by coupling-dependent metabolic ultradian oscillatory manner[37] in support of adaptation, not to mention that Piezo1 plays a critical role in this activation process[38]. Consequently, as a result of proprioceptive terminal Piezo2 channelopathy-induced impaired Piezo2-Piezo1 cross-frequency coupling may instigate feed-forward exaggerated activation mechanism of fibroblasts as well in support of "wound healing". This may be the reason why RBE of DOMS with underlying Piezo2 channelopathy without regeneration periodization may result in taut bands and even muscle fibrosis if chronic Piezo2 channelopathy excessively loaded and prolonged without regeneration periodization. It is also important to note that the proprioceptive[8], ANS[33,39,40], neuroinflammatory[41] and neuroimmune[42] system involvement is all part of these dysregulated and depletory mechanisms from time zero of primary damage onset[2].

The current author proposes that due to chronic Piezo2 channelopathy and longitudinal protein degradation and resultant constantly activated transcription with neurogenic allostatic stress-related loading, not only aging may be induced due to epigenetic alterations, such as the Horvath clock[43] and other epigenetic clocks show, but may even reveal inherited pathogenic variants and mutations, not to mention acquired mutations from infection and environmental factors, leading to accelerated aging.

Impact of Entropic Force and Time

Aging has its dysregulated time encoding that is mostly reflected in circadian disruption. Nevertheless diurnal and ultradian rhythms are important factors as well, and Piezo1 is involved in diurnal regulation[44], while Piezo2 is proposed to be the principal ultradian sensor and modulator[19]. Moreover, it has been suggested that Piezo2 containing enterochromaffin cells innervated by Piezo2 containing gut glutamatergic sensory neurons may initiate an ultrafast long-distance proton-signaled non-synaptic neurotransmission towards the hippocampus via VGULT3 as the backbone of the gut-brain axis[19]. This ultrafast axis, and the proposed wormhole along, may provide the time encoding amplification of other simultaneous wormhole spatial and time encodings, like the suggested proprioceptive one, arriving to the hippocampus[13]. The integrative hub for the spatial and time (and speed) encoding of wormholes and the backbone of brain axes in the hippocampus may be reflected by hippocampal place cells and a hippocampal ultradian clock may be present due to this simultaneous time encodings[45]. Accordingly, hippocampal place cells receive spatial input from the hexagonal lattice of grid cells of the hippocampus[46] that might resemble to a lattice field of theoretical physics. Not to mention that wormholes provide spatial encoding by frequency coupling of two (driven) quantum (oscillator) systems with holographic duality at the two ends, which is suggested to be the Type Ia proprioceptive terminal and the hippocampal hexagonal lattice of grid cells in the case of the backbone of the proprioceptive muscle-brain axes[13]. However, chronic Piezo2 channelopathy, especially in the gut, may induce circadian

disruption as a result of impaired Piezo system crosstalk, leading to impaired ultradian encoding in the hippocampal clock[19,45].

Interesting to note that mutations have been considered as random events in the past. However, the concept that certain information induces entropic force that may determine genetic mutations is emerging[47]. Moreover, it is also proposed that emergent entropic force from gravity is principally modulated by Piezo2[13]. Accordingly, it has been suggested that neurogenic allostatic stress induced excessive overloading of Piezo2 may impair Piezo2's principal (anti-)gravity modulation, leading to Piezo2 channelopathy, transcription activation and pain[13]. Moreover, repeated inducement of Piezo2 channelopathy with the same bout without regeneration periodization may lead to continuously activated transcription and epigenetic modifications, with resultant impaired emergent entropic force modulation and spatiotemporal hippocampal encoding. This may represent an underlying conflict that arises from the second law of thermodynamics (accordingly the entropy of any system remains constant or increase over time) against the second law of information dynamics (it states that entropy remains constant or decrease over time)[48]. Hence, Piezo2 not only fine controls (anti-)gravity, but transduces emergent space-time (and speed) information from gravity by balancing the second law of thermodynamics and the second law of information dynamics. As a result, a stimulated inner universe is updated in the hippocampus in support of proprioception and hippocampal memory (e.g., spatial and associative). This concept would be in line with the stimulated universe hypothesis[49].

Piezo2 channelopathy functionally may take the state as acute-transient, chronic or irreversible[2] due to proton affinity switch or proton reversal[8]. Moreover, this proton affinity switch induced Piezo2 channelopathy is suggested to be accompanied by resultant energy generation switch and switch to evolutionarily lower metabolic pathways, not to mention the switch to the aforementioned activated transcription[8,19]. Accordingly, chronic Piezo2 channelopathy induced chronic switches turn on the avenue to epigenetic modifications and accelerated aging, as the algorithms of epigenetic clocks predict this linear correlation in line with the second law of thermodynamics. However, this predictable aging process may also provide the opportunity for mutations over time.

In support of this switch to evolutionarily lower biological states from information entropy aspect, SARS-CoV-2 variants related computational modeling not only shows that the number of mutations linearly increase, but information entropy of the variants decreases linearly over time[48,50]. Moreover, these correlations between information entropy and time dynamics not only confirms the second law of information dynamics, but makes mutations predictable with a likely underlying entropic force that deterministically instigates these genetic mutations[48]. In response to these findings the current author proposes that this underlying entropic force is emergent from gravity and SARS-CoV-2 infects human uniquely in order to tap into the increased entropy of humans for its own survival in living cells. Intriguingly, SARS-CoV-2 may attain this goal by inducing Piezo2 channelopathy through its attachment to ACE receptors via the ACE-SERCA-Piezo2 channelopathy pathway[51].

Another strong indication that excitatory Piezo2 transduces emergent space-time (and speed) information from gravity may come from heart rate variability (HRV) monitoring. Accordingly, low-frequency (LF) parameter of HRV was theorized to reflect Piezo2 activity level, based on the theorized superconducting low-frequency Schottky barrier diode-like feature of Piezo2[33]. As LF power decreases during medium- to high intensity exercise loading, entropy increases, while at close to zero LF power is when entropy is the highest[24], reflecting a high disorder or chaos. Hence, HRV measurement, more precisely LF power, might reflect Piezo2's (anti-)gravity modulation capacities based on the Piezo2-Piezo2 crosstalk between the proprioceptive system and ANS[24]. Indeed, LF power diminishes with aging, representing decreased regulation of the ANS[52]. Moreover, a recent study not only showed that this counter modulation may be impaired at non-linear dimensions due to DOMS effect[33], but in another HRV study the degradation of this modulating function of Piezo2

was hypothesized based on the observation of age-dependent effect[53], leading to the resultant remodeling of the cardiac system[24].

Bearing in mind, it is worthy to consider the PIEZO2-related arthrogryposis life-span paradox. Inherited PIEZO2 mutations related arthrogryposis, Gordon syndrome and distal arthrogryposis type 5, is not associated with significant life-span reduction as the abovementioned acquired Piezo2 channelopathy theory would predict it. Hence, it seems that if Piezo2 is functionally absent in the development phase then it may not affect the life span of aging, however it still retards growth when it comes to stature and impairs proprioception. In contrast, if early development was guided by functional PIEZO2 then its functionality serves adaptation, while neurogenic allostatic stress-related functional impairment (acquired channelopathy) of Piezo2 later in life may revive growth, in support of remodeling and wound healing, and dysregulated growth due to repeated bout effect without regeneration periodization leads to pathological remodeling, unfinished wound-healing, epigenetic modifications and accelerated aging.

Growth Revival by Piezo2-Hes1 Axis

The author of this paper proposes that the critical loci and mechanistic link between development and later in life revival of growth is the proprioceptive oscillatory glutamatergic fibers on which cell-autonomous neuron-specific processes may prevail on route to (development, adult hippocampal neurogenesis)/neurodegeneration, as earlier theorized[1] and the abovementioned ALS-related GWAS showed[4]. Furthermore, the principle transcription activator on these proprioceptive oscillatory glutamatergic nerve terminals could be Piezo2, however a critical gene should exist in order to fine-tune, and switch on and off neurogenesis regardless of being in developmental or later growth stage. Another reanalysis of an ALS cohort implicated Hes1 in this function[16], and indeed the implicated Hes1 could be considered as a “maestro” in neurogenesis[54]. The oscillation-dependent direct and indirect expression of Hes1, as a basic Helix-Loop-Helix repressor transcription factor protein, is fine-regulated in epigenetic, transcriptional, post-transcriptional, post-translational processes, and by environmental factors throughout neurogenesis[54]. In addition, Hes1 also have a critical role in pro-differentiation and dendritogenesis of hippocampal glutamatergic pyramidal neurons through the NGF-mediated NF-kappaB-dependent pathway, while the sustainment of the very same NGF/TGFbeta-NF-kappaB protective pathway induced expression of Hes1 is essential in the avoidance of neurodegeneration leading to Alzheimer’s disease[54,55]. Consequently, the current author proposes that the ultradian oscillation-dependent Piezo2-initiated proprioceptive glutamatergic fibers through the NGF/NF-kappaB pathway is pivotal for the fine-tuned (ultrafast modulated) induction of Hes1 expression in support of development, differentiation, however this fine regulation is also essential later in life in support of adult hippocampal neurogenesis to serve adaptation, not to mention remodeling. Noteworthy that the sustainment of the NGF/TGFbeta-NF-kappaB protective pathway also comes with increased GABAergic synaptic terminals and dendrite patterning in hippocampal glutamatergic pyramidal cells[54]. This sustained GABAergic interneurons-induced dendritogenesis is telling about chronic Piezo2 channelopathy for the following six reasons. First, it is a feed-forward inhibition process stemming as a result of microdamaged intrafusal glutamatergic proprioceptive Type Ia terminals because its GABA content cannot inactivate (would be a protective measure against pathological hyperexcitation) acquired Piezo2 channelopathy. Second, this feed-forward hippocampal GABAergic inhibition is exerted on the DRG downstream. Third, the ultrafast long-distance proton-based signaling to the hippocampus switches to fast glutamate-based long-distance signaling with delayed onset of pain involvement in the acute transient phase, but the signaling remains as glutamate-based with chronic Piezo2 channelopathy with the involvement of C-fibers[8]. Fourth, the proprioceptive muscle-brain axis is bi-directional, hence GABAergic inhibition could be exerted along it on DRGs[56] from the hippocampus (arthrogenic muscle inhibition). Fifth, this hippocampal GABAergic inhibition, initiated by dendritogenesis of hippocampal glutamatergic pyramidal cells, seems to have a threshold with a time limit of ten years, as the tertiary injury phase of the quad-phasic non-contact

injury model shows[2]. Sixth, Piezo2 channelopathy at proprioceptive terminals is indeed the onsetting peripheral switched/miswired/impaired input source that governs central sensitization of spinal nociceptive neurons[41], as was highlighted[57].

Hes1 is part of Notch signaling pathway and it is implicated in ALS pathomechanism by inactivating this pathway on motor neurons, but activating it on proliferating glial cells and astrocytes[58]. The author of this manuscript proposes that the Notch signaling pathway inactivation on motor neurons is due to irreversible Piezo2 channelopathy induced VGLUT1 disconnection and proton affinity switch. This proton reversal may inactivate vacuolar proton pump (V-ATPase), hence Notch signaling[59] on motor neurons of ALS. However, irreversible Piezo2 channelopathy induced Piezo1 activation due to lost Piezo2-Piezo1 crosstalk and protons will activate Notch signaling pathway in proliferating glia cells and astrocytes of ALS in a dysregulated way.

However, the direct fine modulation could take an indirect path in response to allostatic stress induced Piezo2 channelopathy. As a result, an exaggerated NGF/NF-kappaB pathway induced Hes1 expression is proposed by the author of this manuscript due to lost Piezo2-dependent fine (ultrafast) tuning of ultradian oscillations, as DOMS shows[2,13] and theorized to be depleted on route to neurodegenerative diseases. Hence, ultradian oscillations are not only important underlying mechanism in neurogenesis and adult hippocampal neurogenesis[54], but in muscle stem cell activation as well, controlled by Hes1 through MyoD[60]. Accordingly, these stem cells are regulated by Piezo1[61], but it is suggested that the principal conductor of this fine regulation is through the proprioceptive glutamatergic fibers with Piezo2 in their terminals via Piezo2-Piezo1 cross-frequency coupling in a given compartment[2]. As a result, acute transient Piezo2 channelopathy could induce exaggerated stem cell activation, as could be seen in response to eccentric contractions[62] and DOMS, and explains DOMS-induced muscle gain. Noteworthy, that one suggested unidirectional pathway for proton reversal that is theorized to induce acquired Piezo2 channelopathy is the dissociation of the auxiliary subunit protein MyoD from Piezo2[2,8]. In contrast, irreversible Piezo2 channelopathy terminally depletes the aforementioned exaggerated compensatory process in ALS[16]. Therefore, analogous exaggerated reflex-like compensatory growth induction is proposed at both ends of the impaired underlying ultrafast backbone of the proprioceptive muscle-brain axis in an acute transient form of Piezo2 channelopathy in DOMS. However, the irreversible form Piezo2 channelopathy depletes peripheral muscle stem cell activation due to lost underlying ultrafast backbone of the proprioceptive muscle-brain axis, and consequently dysregulates adult neurogenesis[63].

After all, Piezo2 may not only a principal transcription activator, and ultradian fine sensor and modulator in addition to ultrafast force sensor emergent from gravity and its modulator[2,8,13], but could be viewed as a principal or fine/ultrafast modulator of epigenetics through the “maestro” Hes1, especially under non-linear/perturbed circumstances when the information entropy is the highest.

Anticipatory Synchronization by Piezo2-Syndecans Intrinsically Disordered Domains

In support, non-linearity can indeed feedback fluctuations in order to induce robust oscillations by the self-repressing Hes1[64]. Dynamic system based regulatory networks are both non-linear and inherently stochastic. Accordingly, the stochastic dynamics could switch the gene from its free/inactive to its transcription bound/active state, hence stochasticity induced perturbed noise could be harnessed in order to gain functional information added in regulatory networks[64]. However, prior to stochastic switching a transduction through a low-pass filter should prevail in order for Hes1 to feed-back to itself and impacting the dynamics of genetic networks[64]. This low-pass filter is suggested to be Piezo2 with its low-frequency Schottky barrier semiconductor diode-like feature on proprioceptive glutamatergic neurons[14,16]. Consequently, this mechanism explains how acute Piezo2 channelopathy could be a principal transcription activator and a principal fine/ultrafast modulator of epigenetics through Hes1, and how transcription regulation and non-linear degradation could be simultaneously harnessed as a consequence of chronic Piezo2 channelopathy. However, irreversible Piezo2 channelopathy deterministically result in non-linear degradation. In

favor of detecting this mechanism, HRV measures during DOMS inducing exercise show such non-linear alterations[33], while the aging-dependent non-linear degradation of the theoretical low-pass filter function of Piezo2 could be observed in longitudinal HRV analysis[53]. Off note, the transcription factors of Escherichia Coli are self-repressing as well, like Hes1, from which such dynamics could emerge[65,66], as was hypothesized in colorectal cancer[19].

Another important consideration is the partial synchronization of diffusively time-delay coupled oscillator networks, like the one suggested to arise in the hippocampus[14]. Accordingly, when full synchronization does not occur then the expected collective behavior may not prevail or partial synchronization occurs with no coherent behavior[67]. Hence, some but not all ultrafast ultradian backbone of brain axes synchronize to hippocampal theta rhythm or partially synchronize. This partial synchronization was coined as a switch or miswiring earlier[2] and the time delay represents the propagation speed and time on route to decision making[67]. Consequently, a threshold of coupling strength is implicit in support of full synchronization[67]. Once the coupling strength is not strong enough and/or time-delays are increased then no coherent behavior could be expected as a result of the absent full synchronization of the impacted unit within network synchronization[67]. In support, an aforementioned study demonstrated the MLR of the stretch reflex, suggested to arise from the intrafusal proprioceptors, was significantly delayed as a consequence of DOMS-inducing exercise[10]. Accordingly, the ultrafast ultradian Piezo2-Piezo2 cross-frequency coupling between the intrafusal proprioceptive and hippocampal oscillators may represent such a unit within hippocampal theta rhythm[2,45] and this is why Piezo2 was coined as the principle ultradian cross-frequency coupler[33]. Moreover, local and global/system-wise symmetries may be present in these time-delayed diffusely coupled networks of dynamical units[67]. Correspondingly, local symmetries, including non-symmetric coupling, largely impact the synchronous behavior of these time-delayed diffusely coupled networks[67]. Most systems entail non-linear elements represented in an underlying non-linear time-delay system that may synchronize into a coupled chaotic system[68]. Furthermore, an anticipated synchronization of chaotic systems with time-delay through unidirectional coupling has been discovered[69] and the existence of anticipating synchronization by chaotic semiconductor diode laser has been shown[70]. Noteworthy that Piezo2 was theorized to exhibit a low-frequency Schottky semiconductor diode-like feature[2]. Important to note that the response to postural perturbations are altered [71], orthostasis is impaired[33] in DOMS and mimics a tendency towards a positive Romberg test[72]. This observations may not only imply that an ultrafast switch could be an underlying mechanism as theorized and the aforementioned significantly delayed MLR may substantiate it, but the equivalent of an ultrafast anticipatory synchronization may be impaired that alters the response to postural perturbations. Accordingly, the current author proposes that a co-functional accessory ligand to Piezo2 must be present aside from Piezo2's low-frequency Schottky semiconductor diode-like feature in the earlier proposed superconducting junction[33] in order to serve the non-linear dynamics of the ultrafast non-linear time-delay system that may synchronize in an ultrafast fashion into the coupled hippocampal chaotic system. Piezo2 (intrinsically disordered intracellular domain)[73] and syndecans (intrinsically disordered ectodomains tethered to the extracellular matrix)[74] may exhibit this co-functioning accessory ligand. Moreover, Piezo2 channelopathy/proton affinity switch induced microdamage causes their functional decoupling leading to shedding of syndecans and extracellular matrix rupture, as was theorized earlier[16]. Moreover, this non-linear ultrafast sensing capability why the genetic charge altering variants of syndecan-3 in ALS may have high functional relevance when it comes to Piezo2 channelopathy in disease progression due to the resultant extracellular matrix dysfunction and breakdown as a result of proton affinity switch induced Piezo2 channelopathy[16]. Simply put, this suggested anticipatory synchronization under the chaos of homeostatic allostatic stress may provide ultrafast ultradian proprioceptive protection against perturbations, in contrast to Piezo2 channelopathy under allostatic stress when uncertainties are damaging as a result of significantly delayed partial synchronization.

Angelman Syndrome Indicative of Piezo2 Channelopathy Existence

So far, the most compelling evidence for the existence for Piezo2 channelopathy comes from AS, a neurogenetic disorder hallmarked by motor coordination, cognitive deficits, gastrointestinal dysfunction and seizure[75]. AS is primarily the result of the loss of expression of E3 ubiquitin-protein ligase UBE3A in neurons, but without any known PIEZO2 variants in play[76]. Interestingly, linoleic acid fortified diet enhanced Piezo2 activity and resultant mechano-excitability led to improved gait in AS mice[76]. This finding is in line with earlier theory, based on a DOMS related study[77], that essential polyunsaturated fatty acids may preserve Piezo2 function and prevents DOMS if they are fed preventively[2,41], due to the fact that excitatory Piezo ion channels deplete membrane cholesterol and negatively charged lipids locally[78,79]. However, Piezo2 channelopathy may dysregulate lipid metabolism due to the proposed dissociation of TACAN/TMEM120A from Piezo2[2,16], leading to proton affinity switch and proton reversal induced perturbation in vesicle related transport[8]. Important to note again that the aforementioned ALS-related GWAS also showed perturbation in vesicle related transport[4] and the discrepancy of elevated cholesterol level in ALS was explained earlier. Earlier it was emphasized in relation to DOMS that this transmembrane and extracellular membrane surface negatively charged lipid depletion may alter the electrostatic micromilieu, leading to Piezo2 channelopathy or proton affinity switch/proton (and electron) reversal[8]. Interestingly, the lipoxygenase (and COX2) inhibitory function of diclofenac effectively prevents DOMS evolvment and it is devoted to blocking lipoxygenase's proton and electron reversal promotion through its facilitation of proton-coupled electron transfer (PCET) reaction, hydrogen tunneling and hydrogen atom abstraction capability towards concerted proton tunneling–electron tunneling (PTET) reaction[8]. It is also worthy of note that lipoxygenase also catalysis the deoxygenation of polyunsaturated fatty acids, like linoleic acid[80]. In response to the aforementioned switch of charge in the local electrostatic field may promote conformational changes in enzymes, like in lipoxygenase, leading to shorter donor–acceptor distance in these proteins that is preferential for their efficient hydrogen tunneling and proton transfer[80], contributing to the proposed Piezo2 channelopathy-induced miswiring[2,8]. Therefore, it is suggested that prolonged eccentric/forced lengthening contractions induces Piezo2 channelopathy (dissociation of Piezo2 from TACAN/TMEM120A) leading to proton reversal which inhibits quantum mechanical/molecular mechanical free energy stimulation aspect of Piezo2-initiated ultrafast long-range proton signaling, but promotes miswiring of extracellular protons towards activated lipoxygenase-induced PCET and PTET. Piezo2 channelopathy/proton reversal proposed to impair the vesicular glutamate release[8,81] and this glutamate transport reversal also explains that compartmentalized glutamate leakage that activates the lipoxygenase pathway[82], leading to not only switch to glutamate-based signaling, but to proton miswiring as well[8].

Even more compelling findings in reference to AS from the same authors towards Piezo2 channelopathy that cofilin inhibitor (SZ-3) restituted Piezo2 function in DRG neurons and glutamate-evoked currents in hippocampal neurons, leading to improvement in motor coordination and spatial learning[75]. These results not only show that loss of UBE3A expression induced increased cofilin tagging-related proteasomal degradation of Piezo2 could be prevented by SZ-3 with restituted Piezo2 function, but the restoration of AMPA receptor function in hippocampal neurons by SZ-3 [75] may also reveal that AMPA plays an important role in Piezo2-initiated proton-based ultrafast long-distance signaling, since protons fine-regulate excitatory AMPA information processing in neuronal synapses[83]. After all, may not only force-from-filament and force-from-lipid modulates Piezo2 mechanistically, but force-from-proton as well[8]. Noteworthy that Piezo2 channelopathy may also induces a pain pathway switch due to proton reversal induced lost proton-based ultrafast oscillatory signaling switched to glutamate-based signaling through NMDA receptors[8], and possibly through AMPA. Noteworthy that long-COVID will induce feed-forward AMPA receptor increase[84] likely due to onsetting ACE-SERCA-Piezo2 pathway induced chronic Piezo2 channelopathy, but dysregulated AMPA signaling may also explains cognitive impairment of AS as well. However, the

current author proposed that irreversible Piezo2 channelopathy mainly does not result in switched AMPA signaling, hence mostly does not induce cognitive deficit in ALS.

Moreover, another consideration that people with AS usually have normal lifespan, however complications from seizures and injuries may shorten it. Accordingly, the UBE3A expression induced increased cofilin tagging-related proteasomal degradation of Piezo2 may substantially decreases anticipatory synchronization under allostatic stress induced chaos, leading to increased injury risk. This could be observed in DOMS[41] and may implicit of ALS pathomechanism onset when it comes to repeated head injuries for example[85], but non-contact injuries are likely unnoticed in ALS due to its 'painless' feature. Acquired Piezo2 channelopathy-induced increased L-type voltage-gated calcium channels and voltage-gated sodium channels loading and their progressive degradation may explain AS's increased seizures, as an another ALS analysis shows[86].

Conclusion

Local, compartmental and systemic growth control after all is in line with Hilton's rule by the principle guidance of proprioceptive glutamatergic terminals[87] with Piezo2 content. Acquired Piezo2 channelopathy with its impaired low-pass filter, low-frequency Schottky diode-like features may not only principally activates transcription, but also modulates epigenetics through Hes1 activation especially under non-linear perturbed conditions when information entropy emergent of gravity is the highest. The impairment of the ultrafast detection of these nonlinear dynamics has special relevance not only in growth revival, but in non-contact injuries as well that deterministically accelerate aging in the chronic presence of acquired Piezo2 channelopathy, not to mention in its irreversible form when it comes to ALS.

Important to note that the current paper does not exclude the relevance of the contribution of other ion channels, ligands, auxiliary proteins and lipids, however devotes principality to Piezo2 when it comes to proton-based ultrafast long-distance non-synaptic neurotransmission initiation. However, medical science should seek help form theoretical physics for translational purposes regardless of no unequivocal link exist so far between quantum theory and quantum gravity theory.

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