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Big Bang, Wormholes, and Piezo2 Within Humans

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Article

Big Bang, Wormholes, and Piezo2 Within Humans

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Highlights:

- Principality of Piezo2 may come from proprioception related mechanotransduction by fine or ultrafast regulation of force against gravity, transduced by protons (and electrons).
- Wormholes may connect two distant points through a tunnel in spacetime, like the suggested axis between the instrafusal Piezo2 containing Type Ia proprioceptive terminal and the hippocampus. These wormholes may construct the underlying backbone of brain axes, synchronized by the hippocampus to theta rhythm under homeostatic state.
- The impairment of this non-synaptic long-distance neurotransmission is proposed to be analogous to a Big Bang or acquired Piezo2 channelopathy, and that is the theorized principle gateway to pathophysiology or the one common root cause of aging initiation.
- Theoretical physics should have a place in science when it comes to mechanotransduction, or even more importantly when it comes to proprioception.

Outstanding Questions:

- Is Piezo2 a force sensor? The current manuscript posits that Piezo2 is not only a force sensor, but even fine regulates force from proton in order to counteract against gravity.
- Do wormholes exist in humans? The current manuscript suggests that this ultrafast long-distance signaling should be contemplated despite quantum gravity concept is short of being unequivocally proven to be unified with quantum theory.
- Is Piezo2 the principal mechanosensory ion channel responsible for proprioception? Since mechanostransduction is hierarchical and on top of it the current paper proposes that only Piezo2 is capable of initiating an ultrafast long-distance proton-based quantum tunneling and even inducing wormholes during ultradian events. These enigmatic features may explain Piezo2's principality. However, other ion channels certainly also contribute downstream, like ELKIN1 and auxiliary subunit proteins of Piezo2.
- Is the Big Bang within us? The current paper proposes that it is the acquired Piezo2 channelopathy and that is the theorized principle gateway to pathophysiology or the one common root cause of aging initiation.
- Where is the functional Piezo2 channeloapthy structurally evolves? Is the plug-and-latch mechanism of Piezo2 that is microdamaged or the auxilliary proteins of Piezo2 are detached due to conformational changes? After all it does not seem to matter, because both may result in a proton affinity switch or proton reversal when it should not happen.
- Does theoretical physics have a place in science when it comes to mechanotransduction, or more importantly to proprioception? The current manuscript claims that it is time and inevitable to involve theoretical physics in mechanotransduction and proprioception in order to facilitate scientific development.

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Abstract

Big Bang theories are connected to gravity by force of attraction. Forced lengthening, like eccentric contractions instigate proprioception as a result of working against gravity. Piezo2, as the principle mechanosensory ion channel responsible for proprioception, may fine modulates these anti-gravitational contractions in order to provide system-wide ultrafast postural control. This mechanism instantaneously emits blast energy by Piezo2 in order to offset gravity and it is suggested to be propagated by quantum tunneling of protons (and electrons). However, wormholes should be considered as part of this ultrafast long-distance non-synaptic neurotransmission despite quantum gravity concept is short of being unequivocally proven to be unified with quantum theory. The impairment of this signaling is the equivalent of the Big Bang within a given compartment, or acquired Piezo2 channelopathy, leading to the principle gateway to pathophysiology.

Keywords: gravity; mechanotransduction; proprioception; wormhole; Big Bang; Piezo2 channelopathy

Introduction

Gravitational waves are induced at any oscillatory frequencies by the relative motion of gravitating masses with propagation at the speed of light [1]. Moreover, waves like sound waves and electromagnetic waves propagate energy, momentum and angular momentum away from its origin [1] and gravitational waves are not different either from this aspect. The Nobel Prize was awarded to Rainer Weiss, Barry C. Barish and Kip S. Thorne in 2017 for detecting these gravitational waves. However, the quantum gravity concept is short of being unequivocally proven to unify with quantum theory. Furthermore, it is suggested that the force of gravity evolves as an entropic force and that is the result of changes in the entropy stemming from the positions of material bodies in space [2].

This perspective manuscript is meant to introduce that a "Big Bang" energy blasts exist within the human body in the form of an acquired Piezo2 channelopathy and oxidative phosphorylation (OXPHOS) depletion. As an underlying theory, Piezo2 may function as an ultradian ultrafast sensor and fine modulator to counterbalance energy and force in order to offset gravity. Accordingly, the current author proposes that eccentric, or forced lengthening, e.g., eccentric muscle contractions, could create such an instantaneous gravitational force offsetting counterbalance, instigated by ultrafast high yielding energy generation by OXPHOS derived protons and ATP in order to fine modulate anti-gravitational force and energy by Piezo2 ion channels, e.g., on large fiber oscillatory glutamatergic Ia type proprioceptive terminals. In support, it has been theorized that not only force-from-lipid or force-from-filament principle may count in force-gated Piezo2 ion channel activation and modulation, but force-from-proton as well [3 4]. Noteworthy is that a recent research suggests that Piezo2 might not be the main transducers of force in sensory neurons [5], but the author of the current paper proposes that Piezo2's principality may exactly come from proprioception related mechanotransduction by fine or ultrafast tuning of force and energy against gravity.

Piezo2 and Piezo2 Channelopathy as the Big Bang

Mechanotransduction is the conversion of external physical cues to internal biological and chemical ones. The principle ion channel in mechanotransduction responsible for proprioception is claimed to be Piezo2 [6]. Noteworthy that some scientists question the principality of Piezo2 in proprioception and indeed some other ion channels contribute to it as well, however it is worth to consider that the activation of these channels are in hierarchical order [7] and Piezo2 function is on top of this hierarchy [7]. Accordingly, a recent theory associate this principality that no other mechanosensory ion channel could initiate an ultrafast proton-based long-distance signaling in the nervous system almost instantaneously, like Piezo2 [8]. Interestingly, the same paper, that questions Piezo2 as the main transducer of force in sensory neurons, shows that the presence of PIEZO2 is

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needed among mechanically-gated channels for the very fast current activation [5]. Proprioception, the timely conscious and unconscious positional sense of our extremities, had been a mystery as our "sixth sense" for almost 200 years, when Sir Charles Bell described it in 1830. Therefore, the Nobel Laurate Ardem Patapoutian and his team made a major contribution to bring proprioception to light by identifying Piezo proteins, and especially Piezo2 [6].

Piezo2, and its related Piezo2 system, has been postulated to function like an "airbag" [8 9]. Correspondingly, once the ultrafast crash sensors of "airbags" face above threshold rapid changes of speed and other stimuli, like compression/indentation and stretch, from collision then an inflator is ignited and inflates a bag within milliseconds in order to counter-cushion and protect the affected individual against gravity and direct injury. Indeed, the intrinsically disordered domain 2 (IDR2) of Piezo2 protein structure is in control of velocity sensitivity of tactile stimuli, while IDR5 and IDR4 controls membrane indentation and pressure-induced membrane stretch stimuli respectively [10]. However, the bag deflates immediately right after the crash and as a result the impact is absorbed. Let's consider that non-contact injuries, like the vast majority of anterior-cruciate ligament injuries (ACL) and delayed-onset muscle soreness (DOMS) - also suggested to be a non-contact injury[7] -, entail a similar underlying primary damage mechanism, where the microdamage of Piezo2 function may evolve [7]. As an analogy, strenuous or/and unaccustomed eccentric contractions under acute stress response (ASR) induced over-excessive stretch (which is also compression on the Piezo2 containing annulospiral terminal of proprioceptive nerves in the muscle spindle) in the case of DOMS [9], and excessive axial compression force under ASR in the case of non-contact ACL injury would be the initiating microdamage that ruptures the airbag, the equivalent of a Big Bang, or an acquired Piezo2 channelopathy [7]. This "rupture" is proposed to be a "proton affinity switch" or "proton reversal" on Piezo2 in association with OXPHOS depletion [4 7 8]. As a consequence of the lost "airbag protection", the selective barrier of the muscle spindle will be compromised due to the impairment of Piezo2-Piezo2 and Piezo2-Piezo1 crosstalk [7]. Consequently, intact Piezo2 containing proprioceptive terminals of muscles spindles are the airbags of the extrafusal muscle space. However, this bi-compartmental mechanism not only exist in muscles, but in the skin where the airbag is the Merkle-cell neurite complex, or entheseal compartments are the airbags for the spine, or enterochromaffin cells and their glutamatergic sensory nerves innervation are the airbags for the gut [7]. Therefore, non-contact injuries cannot prevail in the presence of intact airbag or somatosensory/proprioceptive terminal Piezo2, and consequently acquired Piezo2 channelopathy presents the proposed Big Bang.

Compartment, Wormhole, Recoil Energy, Entropy

The aforementioned glutamatergic Type Ia proprioceptive terminals are located within the muscle spindles and surrounded by fluid cavity with proposed functional relevance, and these muscle spindles are encapsulated by selective barriers [11]. It is important to consider that Piezo2 can sense pressure pulse transduction and this transduction could set in motion through a closed rigid fluid filled compartment, or chamber, almost right away at the speed of sound in agreement with the Pascal's law [12]. The Piezo2 containing muscle spindles, the gastrointestinal tract, the skin, entheseal compartments of the spine, the cornea, the circulatory system, the atrium and ventricle of the heart and the brain are such compartments or chambers as well [7]. Therefore, compartmentalization with selective barriers are important, however largely unaccounted underlying functional structures of the nervous system. Moreover, these compartments are suggested to be in functional cross-communication and principally coupled through or cross-frequency coupled by the Piezo system that entails the Piezo2-Peizo2, Piezo2-Piezo1 and Piezo1-Piezo1 cross-talks [7]. Proprioceptive pseudounipolar Ia sensory afferents evidently connect the muscle spindle to the spinal cord with closed-gate by the intact blood-spinal cord barrier (BSCB) function under homeostasis [11]. Moreover, the fluid filled cavity containing muscle spindle under stretch is an analogous closed rigid fluid filled compartment, as mentioned above, like the spinal cord and it is functionally connected to the brain in a similar fashion. Accordingly, the pressure pulse detection is propagated by the force- and stretch-

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gated Piezo2 content of the peripheral terminals of intrafusal Ia proprioceptive afferents [13] at the speed of sound [12]. As a result, Piezo2 induced principle proprioceptive signaling is suggested to be transduced in a novel ultrafast and long-range fashion with the assistance of oscillatory glutamatergic Ia afferents toward the Piezo2 containing hippocampus via quantum tunneling of protons with the involvement of VGLUT2 and to motoneurons through VGLUT1 [4 7 14]. This ultrafast Piezo2 initiated non-synaptic long-distance neurotransmission toward the hippocampus is suggested to evolve along ultradian events as the ultrafast backbone of other brain axes, like the eye–brain, auditory/vestibular–brain, and proprioceptive muscle–brain axes [15 16].

Important to note the distinct feature of eccentric or lengthening contractions that they come with higher cortical excitation and lower motor unit discharge [17 18]. In addition, eccentric contractions absorb energy from an external load [19], support the body against gravity, absorb shock, and store recoil energy from ground reaction force (GRF) for accelerating contractions [17 20]. They have been also depicted as negative muscular work [19]. However, the problem arises when the storing of energy from the external load, coming from the eccentric contraction-based accelerating movement, cannot "recoil" in the decelerating movement due to the aforementioned "ruptured airbag" or acquired intrafusal Piezo2 channelopathy and resultant selective barrier disruption [21]. Consequently, the excess "unrecoiled" energy coming from accelerating eccentric movements may be partially absorbed by muscles and other tissues, like connective tissue, fascia and extracellular matrix in a damaging way as part of the secondary damage [21]. In support, it has been proposed that damaging eccentric exercise is to blame for the impairment of proprioception [22]. Indeed, one cardinal symptom of DOMS is impaired proprioceptive function right after eccentric exercise, proposed to arise from the muscle spindle [23]. Therefore, the aforementioned antigravitational ultrafast fine-tuning feature in association with eccentric contractions may arises from Piezo2 containing proprioceptive loading with the involvement of the stretch reflex [24].

After all, it is worthy of consideration that the ultrafast Piezo2 initiated non-synaptic long-distance somatosensory neurotransmission toward the hippocampus along ultradian events may be analogous to an Einstein-Rosen bridge or a wormhole. Wormhole is a link between entanglement and gravity, as theorized by quantum gravity. Accordingly, these wormholes may connect two distant points through a tunnel in spacetime, meaning travel in space and time, and collapses almost instantly in the absence of negative energy [25]. Noteworthy, there is no unequivocal evidence that wormholes exist [25] and certainly no proof of link to quantum theory. However, these unstable tunnels may transduce information in a coordinate system. Important to note that the clock of the two ends of such a wormhole may always kept synchronized regardless of how the ends move in space, hence the constant time allows space-like separation on a surface. Notable that earlier it has been proposed that Huygens synchronization contribute to the synchronized state along the novel ultrafast Piezo2 initiated non-synaptic long-distance somatosensory neurotransmission toward the hippocampus [14], based on the work of Kocsis et al. [26]. Moreover, wormhole frequency coupling also exists in theoretical physics where holographic duality may arises from the coupling in between two quantum systems [27]. This is also in line with earlier theory that proton-proton frequency coupling through VGLUT2 may provide the ultrafast Piezo2 initiated non-synaptic long-distance somatosensory neurotransmission toward the hippocampus [14]. In support, conditional knockout VGLUT2 mice exhibited remarkably different oscillatory activity in the hippocampus with impaired spatial memory [28]. Above all, this mechanism theory entailing Piezo2 initiated wormholes not only could explain hippocampal spatial memory, but muscle memory as well due to holographic duality. Furthermore, these Piezo2 initiated wormholes may present the ultradian backbone of brain axes, not to mention the suggested ultradian clock of the hippocampus [15 16]. Moreover, Piezo2 initiated wormholes may provide peripheral spatial and speed inputs to the space and speed coding of the hippocampal theta rhythm, supporting locomotion, learning and memory, as was theorized earlier [14].

PIEZO2 is critical in the defensive arousal response (DAR) as a recent traumatic brain injury (TBI) research showed [29]. Important to note that the whiplash nature of mild TBI is suggested to have an analogous bi-phasic non-contact injury mechanism, like DOMS and non-contact ACL injury,

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where the primary damage may arise from acquired proprioceptive neuron terminal Piezo2 channelopathy as well [7]. DAR is essential for survival, and it is turned on by a perceived threat and evoked by visual and auditory cues in the presence of motor abilities [29]. DAR may be analogous to ASR and that is part of the neurocentric acquired Piezo2 channelopathy theory of DOMS and non-contact ACL injury [7] and might be often induced e.g., during competitive game situations. Interestingly, a recent preprint paper proposes the proton-based ultrafast matching/synchronization of the Piezo2-initiated eye–brain, auditory/vestibular–brain, and proprioceptive muscle–brain axes within the hippocampal hub[30], in line with the abovementioned PIEZO2-related DAR mechanism. Indeed, earlier research showed that sensory input could be temporally organized by ultradian brain rhythms in concert with temporary synchronization of the heart rate, medulla firing and the hippocampal theta rhythm [31 32]. Accordingly, the PIEZO2-related DAR study may highlight the ultrafast ultradian sensory and ultradian rhythm generation function of Piezo2[33] in order to support postural stability instantaneously against gravity under DAR/ASR. This may explain why DOMS alters the response to postural perturbations [34] and significantly increases the medium latency response of the stretch reflex [35], as a result of the suggested acquired Piezo2 channelopathy. Indeed, the aforementioned research paper revealed that in the absence of PIEZO2 the very fast neuronal current activation among mechanically-gated channels was reduced[5], in support of the theorized ultradian ultrafast sensory function of Piezo2 [7]. Therefore, the proposed Piezo2 initiated wormholes under DAR/ASR may not only analogous to the theorized underlying Piezo2-initiated proton-based ultrafast ultradian hippocampal backbone of eye–brain, auditory/vestibular–brain, and proprioceptive muscle–brain axes, but they may temporarily synchronized to the hippocampal hub and theta rhythm as well. Nevertheless, acquired Piezo2 channelpathy may impair this fine tuning of Piezo2 initiated ultrafast ultradian hippocampal synchronization, leading to reduced ability to respond to ultradian events, especially perturbations, therefore increasing injury risk, as is the case in DOMS for example [7].

Piezo2 has been called as the principle cross-frequency-coupler, or entrainer, under allostatic stress [33]. Accordingly, an additional ultradian brain axis (wormhole) contribution should be considered within ultradian rhythms and that is the ultradian heart-brain axes in support of fine control of autonomic nervous system (ANS) regulation through Piezo2-Piezo2 crosstalk in a heart rate dependent manner [33], fully in line with earlier observation of Pedemonte et al [31 32]. Important to note that Piezo2 channels have been associated with low-frequency Schottky semiconductor barrier diode-like function [14], moreover with a super-Schottky diode one [33]. Paired-associative electromagnetic stimulation, including both transcranial and peripheral, after DOMS-inducing exercise had a positive therapeutic impact not only on DOMS related symptoms, but on heart rate variability (HRV) parameters, reflecting the ANS's involvement in the impairment [36 37]. This is in contrast to only peripheral electromagnetic stimulation when the treatment proved to be ineffective in DOMS [38]. Supportive finding of the Piezo2 channelopathy involved neurocentric DOMS theory[7], and the abovementioned therapeutic effect of paired-associative electromagnetic stimulation[36 37] that Piezo2 is found to be the underlying precise/fine mediator of magnetic stimulation[39], as was suggested earlier[7]. Presently it is an unattainable challenge to create a man-made gravitational wormhole due to the large negative gravitational energy demand. Nonetheless, magnetic materials with superior magnetic permeability, including superconductors, led to the remarkable scientific accomplishment that magnetic wormhole was constructed in laboratory settings [40]. Noteworthy that magnetic wormhole is not identical to the Einstein-Rosen bridge (gravitational wormhole), however also connects two distant points to allow electromagnetic wave propagation via a magnetically undetectable and invisible tunnel, hence underscoring the feasibility of the proposed ultradian ultrafast Piezo2 initiated non-synaptic long-distance neurotransmission.

The question rightly arises where the negative energy come from in order to induce a wormhole. As mentioned above, forced lengthening contractions also coined as negative work mainly stemming from GRF. In order to understand the metabolic and energy generation mechanism of eccentric contractions, it is worth to consider that Piezo2 may modulate the reactive oxygen species (ROS)-

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dependent mitochondrial high frequency oscillations, and Piezo2 channelopathy might fail to do so [33]. In support, DOMS increases ROS production [41] and recent Piezo1-related research also show there is a link between Piezo ion channels and oxidative modulation[42], however the current author proposes that Piezo exerts fine oxidative modulation and not the other way around. Furthermore, ROS have a dual role both in hippocampal learning and memory, and in hippocampal neurotoxicity and even neurodegeneration [43 44]. This dual role of ROS is also present in the mitochondria of the heart as well [45], and may not only telling about the underlying Piezo2 initiated wormhole (backbone) of the heart-brain axis, but about the Piezo2 crosstalk coupled to the ANS [16]. Piezo2 channelopathy theory posits that the primary damage may evolve at nerve terminals, like the Type Ia proprioceptive one, where the mitochondria content is high, reflecting the high energy demand [11]. In addition, on route to this hypothetical microdamage is the critical pathway of electron leakage serving ROS production primarily through the electron transport chain [11 14] and proton motive force [4]. Piezo2 channelopathy theory proposes that it may come with a proton affinity switch [4], hence it might explain the dual role of ROS [33]. Acquired Piezo2 channelopathy was even hypothesized to be the principal gateway to pathophysiology, or the primary damage and that is suspected to be the one common root cause of aging initiation [7]. In accordance with the dual role of ROS, increased ROS production may explain the inducement of the inflammatory reflex within homeostasis in support of remodeling, in contrast to proton affinity switch that may induce the gateway reflex as a breach of remodeling [7]. Accordingly, Piezo2 channelopathy may not only instigate a proton affinity switch, leading to neural switch or miswiring, but may also impair quantum tunneling of protons and electrons from mitochondria [4], leading to increased ROS production, and resultant increased entropy and accelerated aging [33]. Correspondingly, this pathophysiology is analogous to the one observed in aging of brain mitochondria [46], but parameters of HRV, like nonlinear ones as entropy is, also reflects upon the age dependence of HRV of the heart, translated as due to age-related degradation of Piezo2 [47]. Finally, it is also worth considering that proton affinity switch might explain why reverse electron transport could prevail [33]. Indeed, mitochondrial ROS production is increased by reverse electron transport [48]. Piezo1 is essentially involved in force-induced ATP secretion [49], as predicted in the case of Piezo2 as well [15]. Moreover, this force-induced ATP efflux may be coupled to proton motive force generation, while the theorized proton affinity switch or Piezo2 channelopathy may result in transient OXPHOS depletion and the loss of proton motive force generation [4].

Symmetry-Breaking, Non-Linearity, Good Stress, Bad Stress – Selye Was Right

It has been proposed that the proton-release capability of Piezo2 is symmetry-breaking, leading to the collapse of the disordered symmetric state in order to accomplish an ordered, but not symmetric state as excitation increases along acute intensive exercise loading [33]. The current author posits that this distinctive feature of Piezo2 may allow it to respond to ultradian events in an ultrafast fashion under DAR/ASR. The quantum mechanical outcome of symmetry-breaking in reference to wormholes that it transforms from a harmonic oscillator wavefunction to a spectrum of quantum state [50]. This transformation of wormholes to quantum state may be important to prioritize and differentiate the stress induced higher loaded/excitated ones, e.g., prioritizing the intrafusal proprioceptive one from the aforementioned other ultradian sensory wormholes (backbone of brain axes) that are temporally organized by ultradian brain rhythms in coordination with temporary synchronization of the heart rate, medulla firing and the hippocampal theta rhythm. This transformation of wormholes to quantum state may allow to enhance hippocampal spatial encoding and memory in a differentiated way under DAR/ASR in order to enhance the precision of ultrafast memory and spatial representation in support of proprioception under a DAR/ASR [51].

The metabolic footprint of this space-time-dependent inhomogeneous perturbation of biochemical instability is diffusion induced symmetry-breaking [52]. Accordingly, glycolysis may be considered as a spatio-temporal dissipative structure based on diffusion, leading to the form of sustained oscillations [52]. The current author suggests that the symmetry-breaking of wormhole that transforms from a harmonic oscillator wavefunction to a spectrum of quantum state, may also induce

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a symmetry-breaking in the wavelike pattern of glycolysis by upregulating OXPHOS. However, proton affinity switch or Piezo2 channelopathy may switch to a state when glycolysis is preferentially used over OXPHOS due to OXPHOS depletion [4]. More precisely the resultant impaired intracellular proton gradient may switch mitochondrial energy metabolism from the evolutionarily superior energy-generating OXPHOS and glutamine respiration pathways to the mitochondrial glucose and glutamine fermentation pathways [4]. During fast growth, this glucose and glutamine respiro-fermentation could run parallel, like in cancer [53] and immune cells [54]. The author of this paper suggest that the resultant derailment of ATP and ADP concentration may cause further stress on the affected cell and associated mitochondrial destabilization that conserves the symmetry-breaking and the non-equilibrium phase transition until Piezo2 channelopathy is sustained. This is in line with the explanation of Sel'kov model of glycolysis as a spatial dissipative symmetry-breaking instability structure [52].

However, the current author also proposes that it is important to distinguish four hierarchical phases of energy generation under allostatic stress. One, when OXPHOS and glutamine respiration pathways are coupled, or the equivalent of harmonic oscillator wavefunction of the wormhole. Second phase, when OXPHOS and glutamine respiration pathways are de-coupled. This decoupling is the equivalent of transformation of the wormhole from a harmonic oscillator wavefunction to a spectrum of quantum state and this symmetry-breaking in the wavelike pattern upregulates OXPHOS. In this second phase, recoil energy may not be stored efficiently anymore in the form of ATP and proton motive force, hence eccentric contractions become damaging. The third phase when Piezo2 is inactivated, but symmetry-breaking of the quantum state of the wormhole is sustained due to the switch to secondary proprioception, namely to Type II intrafusal fibers with ASIC3 content, with underlying heavier metabolic duress and wormhole instability. The current author also proposes that this might be the moment when intensive physical exercise shifts the brain away from theta rhythm towards gamma and beta rhythm. The fourth stage is the suggested Big Bang, or Piezo2 channelopathy when the proton affinity switch not only depletes OXPHOS, but shifts glycolysis and glutamine respiration pathways towards the mitochondrial damaging glucose and glutamine fermentation pathways [9]. This fourth stage may not only cause the collapse of the wormhole, but cannot be induced again until Piezo2 channelopathy is present, therefore the fine (ultrafast) control of anti-gravity protection may lack for the time being. This is why DOMS is not only associated with skeletal mitochondrial damage[55] due to metabolism and energy generation switch[4], but alters the response to postural perturbations[34] and mimics a positive Romberg-test due to impaired fine (ultrafast) control of proprioception [30]. Moreover, damaging eccentric contractions and DOMS increases insulin resistance[56], impairs orthostasis in a diabetes-like manner[57], and alters HRV due to impaired fine (ultrafast) control of insulin sensitivity[7] and the ANS respectively [33].

Noteworthy that ultradian oscillations in the plasma level of glucose and insulin is evident in non-diabetic individuals [58], while these oscillations are decreased and less controlled in diabetic patients [59 60]. One interesting study applied a mathematical non-linear two-delay model on glucose regulation mechanism and showed that stochastic effects may also contribute to this regulative mechanism [61]. In support, DOMS related studies not only found impaired orthostasis in a diabetes-like fashion[57], but detected non-linear alteration in HRV as well [33].

Nerve growth factor (NGF) also subject to ultradian oscillations in the plasma levels of healthy individuals [62]. The scientific debate of what comes first exists in science in regard to the primary damage of DOMS, where one side demonstrated that increased NGF initiates the pathophysiology onset [63]. The other side of the debate however theorizes that acquired Piezo2 channelopathy comes first followed by increases of NGF production by mesenchymal cells[4]. This elevated NGF production could be the result of sensory terminal Piezo2 channelopathy-derived switched/miswired signaling and impaired cross-frequency coupling of Piezo2–Piezo2 and Piezo2–Piezo1, leading to impaired Piezo1-driven cell orientation and adjustment [4]. Notable that NGF is essential for neural survival, growth and maintenance, while shows decline with aging [64].

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János (Hans) Selye coined good stress as eustress and bad stress as distress [65]. Accordingly, two states of Piezo2 may persist under allostatic stress. Inactivated intact Piezo2 under allostatic stress represent "coupled" (intact Piezo2 crosstalk) good stress, while the acquired microdamage of Piezo2 may represent "decoupled" (impaired Piezo crosstalk despite modulation is taken over by secondary proprioceptive ASIC3 as an adaptive mechanism) bad stress [33]. In support, evolutionarily conserved Piezo buffers mechanical stress through modulation of intracellular calcium handling in Drosophila heart and the functional mutation of PIEZO fails this mechanical stress buffering, leading to pathological remodeling [66]. After all, impaired low-frequency Schottky semiconductor barrier diode-like feature of Piezo2 likely fails to modulate ROS induced high-frequency oscillations, but even more importantly may fail to initiate quantum tunneling of protons (and electrons) and might fail to induce wormholes as a result of Piezo2 channelopathy or a Big Bang.

Conclusions

The quantum mechanical background in regard to non-synaptic neurotransmission within the central nervous system is emerging to be evident[46] and its relevance is also emerging on the periphery [4 14]. However, the Piezo2 initiated novel ultrafast non-synaptic neurotransmission within the nervous system may also take the forms of wormholes towards the hippocampus. These wormholes may contribute to the ultrafast backbones of the brain axes. The absence or impairment of these wormholes may result in a switch/miswiring in the nervous system and resultant impaired brain axes downstream. The theoretical proprioceptive wormhole in between the intrafusal Type Ia terminal Piezo2 and the hippocampus suggests that Piezo2 may serve as anti-gravity fine modulator. Moreover, the microdamage of Piezo2 function may not only cause proton reversal (even electron reversal), but might be equivalent to a Big Bang. The acquired Piezo2 channelopathy theory posits that there is no non-contact injury in the absence of the functional microdamage of terminal somatosensory Piezo2, coined as the primary damage, and may evolve not only in DOMS, but on Piezo2 containing somatorsensory terminals contributing to proprioception under forced lengthening and allostatic stress, like in the skin, spine, and gut [7].

The link between the quantum gravity concept and quantum theory is short of being unequivocally proven, however they seem to describe the same process. This scientific challenge seems not only the question of physicist, but the current author suggests that it is the challenge of medicine as well. Hence, the introduction of theoretical physics in mechanotransduction and proprioception seems to be inevitable in order to facilitate scientific development.

Finally, the current author proposes that only acute intensive exercise moments and DOMS provide the opportunity to examine the system-wide effect of acquired Piezo2 channelopathy, since Piezo2 initiated pathways are microdamaged, degraded and degenerated by the time patients visit their doctors with their complaints and pain conditions.

One of the most fundamental structural question whether Piezo2 channelopathy entails the direct microdamage of the plug-and-latch mechanism of Piezo2[67] or the indirect dissociation of auxiliary subunit proteins of Piezo2 [7]. After all it does not seem to matter, because both may result in a proton affinity switch or proton reversal when it should not happen.

Piezo2 channelopathy is an especially intriguing area of future research, because the resultant switch within the nervous system, involving the hippocampus as the site for adult hippocampal neurogenesis, could be one key mechanism leading to accelerated aging and neurodegeneration.

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