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A unifying hypothesis for delirium and hospital-acquired weakness as synaptic dysfunctions

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ABSTRACT

In this paper, we discuss a unifying hypothesis, supported by Hebbian theory, that postulates that both delirium/toxic-metabolic encephalopathy (DTME) and hospital-acquired weakness (HAW) obey to a similar underlying anatomic site of dysfunction: the synapse. A brief historical and current state of endorsing knowledge summarizing its plausibility is presented. Both DTME and HAW are commonly encountered conditions in clinical practice. It is estimated that up to 30–70% of hospitalized patients will develop DTME and/or HAW. The currently available explanations in the pathophysiology of these conditions vary widely, and there is no consensus explanation on their etiopathogenesis. The disease state itself, inflammation, exo- and endo-toxins and decreased use of the synapse leads to their dysfunction which likely extends to other key cells in the micromilieu such as microglia, astrocytes, capillaries, Schwann cells, oligodendrocytes, and the blood brain barrier, all of which participate in the homeostasis and wellbeing of the synapses. Additional disruption of the micromilieu or presence of synaptotoxins (such as benzodiazepines, cytokines, anesthetics, and others) would allow entry into the neural tissue that could induce, aggravate or accelerate the synaptic dysfunction. As we enter the era of the connectome and synaptome, the Hebbian-endorsed synapse-centered hypothesis (heterogenous neuronal microdisconnections) attempts to unify the hypotheses of delirium/toxic-metabolic encephalopathy and hospital-acquired weakness into a single etiopathomechanism.

Introduction

Delirium/toxic metabolic encephalopathy (DTME) and hospital-acquired weakness (HAW), are common in-hospital clinical conditions [1,2] They have been observed at the bedside to have a strong tendency to coexist [3].

In 1913, just as the synapse had been discovered by Ramon Y Cajal (1892), named by Sherrington (1897), and acetylcholine discovered (1914), Dr Henry Shaw hypothesized the delirium may be a form of "interneuronic synapse" disease [4].

There are an estimated 100 billion neurons in the adult human brain, totaling around 0.15 quadrillion "at-risk" synapses [5]. A central nervous system (CNS) neuron can have an excess of 5000 synapses spread in 3-dimensional space (3D), and functioning in the ever-present time dimension (4D). There are about 1 billion neurons in the spinal cord. A small percentage are alpha-motor neurons (AMN) – the main effectors in the peripheral nervous system (PNS). Appraised is that the lumbosacral cord has about 60,000 AMNs. And, it is calculated that there are approximately 150–180 synapses on each AMN (range 50–2000), and 2–2000 muscle fibers per motor unit, depending on the specific muscle and its function.

There is clinical suggestion that the (CNS) neuronal dysfunction in DTME is widespread, indicating not [just] thalamic and cortical dysfunction [6]. Some authors have focused their explanatory efforts on areas of brain function affected [7], others on the type of neurotransmitters [8], and their chemical topography, and still others have sought the explanation in the locally or remotely generated inflammatory mediators [1,9–11].

These synapses (inhibitory, excitatory, modulatory, motor, sensory, autonomic, etc.), neuron-by-neuron, are at risk of dysfunction. Some synapses, by virtue of use, topography, chemical stresses, aging, plasticity and other factors, will be stronger than others. It seems safe to assume that the stronger the synapses, the more resistant to involution/regression, and more likely to rebound and recover after a period of disuse. However, weaker, hypoactive or inactive synapses follow a pattern of involution given by their imparted strength from use, and are prone to losing function and connection following their "strength gradient" faster and potentially to a point of irreversibility. Decreasing the

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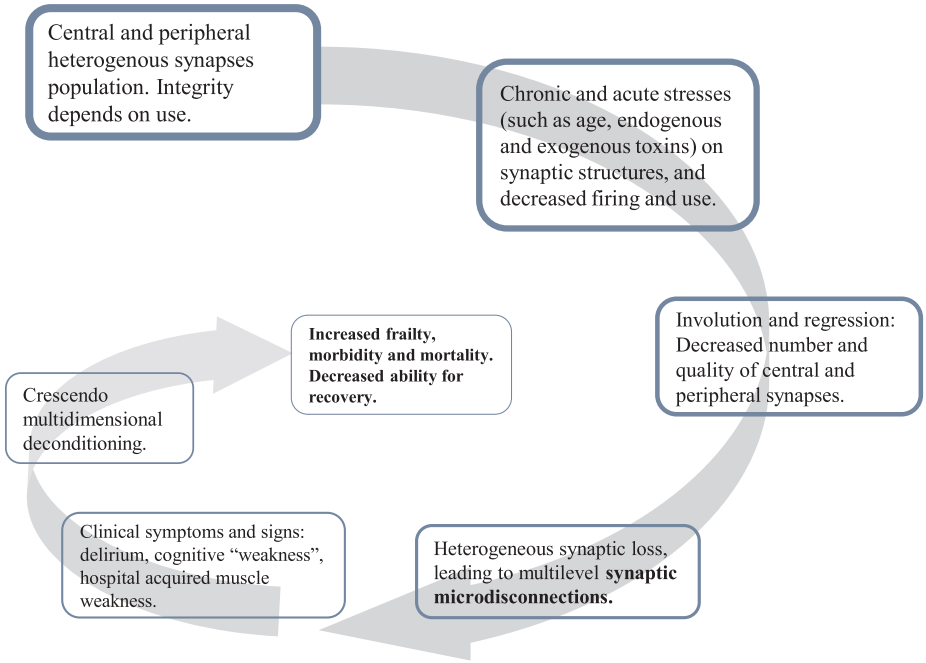

Fig. 1. Hypothesized series of events leading to delirium/toxic metabolic encephalopathy and hospital acquired weakness.

number and fortitude of the anatomic, functioning and effective synaptic units leads to the notion of range or spectrum of synaptopathies with heterogenous severities, on a cell, and in the algorithms of the neural circuits.

Consequently, if the "symphony" of arriving impulses (inhibitory and excitatory) is off time, the effect is a larger wave of dyssynchrony marching through the parallel, in-series and collateral circuitry streams. The dyssynchrony is evident in electroencephalography (EEG) as generalized slowing, and frequently decreased amplitude of the cerebral electrical activity – indicating, in part, altered neurotransmission [12].

Clinically affected are many, if not most, cerebral functions, such as attention, sleep, awareness, circadianicity [13], chronesthesia, emotions, perceptions, delusion, hallucinations, tremulousness/motor, language, thought process, executive functions, cognitive speed/slowing, stimulus processing, behavior generation/modulation, memory, visuospatial orientation, sensory distortions, etc. Also noted, are the re-emergence of primitive reflexes such as grasp, glabellar, Babinski, and others [14]. Virtually every element of synaptic function in the CNS.

In the PNS, it is possible that these muscle dysfunctions are reflective of reduced acetylcholine release, a reduced ability of the post-synapse to respond to the same amount of acetylcholine input, or a combination of both [15]. Exercise enhances neuronal function [16], in a very similar but opposite effect of lack of exercise. Such may be the case in acute, forced sedentariness – as occurs in critical illness. Early physical activity has been promoted as means to increase early (but not long-term) recovery, decrease weakness and enhance recovery in critical illness [17]. On electromyography, critical care weakness is associated with decreased compound muscle action potentials, and preserved or only slightly decreased nerve conduction velocities [18], as well as decreased skeletal muscle excitability [19], suggesting that the main issue is at least in the synapses.

Previously, it might have seemed frugal to suggest that the diverse stimuli, which ultimately trigger synaptic degeneration, may do so through a single, critical step or pathway. The identification of such a step could possibly result in a significant breakthrough in our understanding of why synaptic units are particularly vulnerable, and assist in the development of clinical strategies that protect synaptic function. Possibly providing answers for a broad spectrum of disorders. The methodology behind the synaptic disintegration is found in the difficult to study 4-dimensional (4D) in-vivo, dynamic neurological function. In the CNS the heterogenous and dyssynchronous synaptic involutions or regressions may manifest clinically as DTME, and in the PNS as HAW. Clinically, the loss of synaptic function may seem to occur faster than the recovery of the neurological circuit, causing a sort of accelerated system aging. Aging affects the brain tissue, including the synapses – both in the central and peripheral nervous systems [20]. Although DTME and HAA can occur in children [21], they seem more common in older patients, already with decreased functional reserve.

There are a variety of clinically encountered events, such as motor and cognitive paresis, because of disease or because of medications (such as sedatives, steroids, benzodiazepines), that may accelerate the synaptic dysfunction. For example, steroids have been associated with both delirium and HAW [22], and they are known to induce apoptosis, which may translate in synaptic dysfunction, regression, involution and impaired recovery. Further, neuromuscular drugs, which do not penetrate the CNS, essentially induce paralysis of the neuromuscular junctions, and are well known risk factors for HAW [23]. Their use has been associated with DTME, which may be CNS dysfunction secondary to the motor immobility they induce.

Hypothesis

We hypothesize that the epicenter, in the etiopathogenesis of both DTME and HAW is at the level of synapses, and that of Hebbian spike-timing dependent plasticity (STDP), "use it or lose it", is the key mechanism in the neurodysplasticity and in the heterogenous micro-disconnecting synaptopathies that lead to the frequently overlapping clinical syndromes (see Fig. 1).

Background

Multiple sequential, parallel and temporal mechanisms that occur during the neural pathway function, such as patterns of interacting waves, low threshold Na+ spikes and high threshold Ca+ spikes [24], postsynaptic N-methyl D-aspartate (NMDA) receptors and mGluRs receptors [25], impairment of mitochondrial transport [26] have been postulated to drive the specialized intercellular junction in which a nerve impulse passes to excitable cells, the synaptic unit. Intense and

ongoing research, on the complex operations of live synapses has remained difficult, in part due to the diverse variety of synapse types, locations, uses, chronometry, chronobiology, intrinsic longevity, state of the micromilieu, and because of multiple other underlying factors that have been thought to contribute to the neuronal junction integrity, some of which can be fleeting.

Synaptic ontology is based on the hierarchical description of structures and functions that underlie many biological processes. These functions are known to play key roles in spatial and temporal information processing in the nervous system, such as neurotransmission, confirming that synaptic declension is key to the initiation and progression of disease processes throughout the brain [27]. However, to prevent synaptic decline, these plastic junctions are under biologically strict bidirectional homeostatic control. These processes have also been thought to counteract the instability generated through Hebbian forces, adjusting dendritic appearances, synaptic strengths and intrinsic neuronal excitability, which keeps neural circuits functioning in biologically dynamic and heterogeneous ranges. A precise temporal interval between post and presynaptic spikes will determine the magnitude of the long term potentiation (LTP) or long term depression (LTD) of the synapse [28].

Mitochondria are highly dynamic organelles that divide, fuse, and move within axons and dendrites, mediating regulation of ion homeostasis, stress responses, cell survival and most significantly signal transduction [29]. Neuronal synapses are highly enriched with mitochondria in order to fulfill the high energy requirements needed to fuel the active processes of synaptic transmission, producing the ATP for synaptic ion function and phosphorylation reactions. ATP production by the mitochondria is imperative to maintaining synaptic transmission within the synapse, as mitochondria are essential for calcium ($Ca+$) homeostasis [30].

Changes in mitochondrial functions ($Ca+$ regulation, energy metabolism, and oxyradical production) plays a key role in synaptic plasticity. Age-related cognitive impairment, and presumably the synaptic plasticity subserving learning and memory, is associated with structural abnormalities in mitochondria and oxidation of RNA and DNA. A study by Kawamoto et al (2012) has unveiled the importance of the specificity of $Ca+$ in homeostatic and related signaling machineries. They postulated that $Ca+$ levels underlie the unique responses to the same stimuli of different neurons, accounting for, at least partially, the selective impairment of neuronal subtypes and brain areas observed during aging and neurodegeneration, [30], and putatively in DTME and HAW. The regulation and the release of neurotransmitters from the presynaptic terminals influences both LTP and LTD. The increased $Ca+$ levels in dendrites appear central to synaptic loss, destabilizing the cytoskeleton of dendritic spines, allowing them to involute. The impairment of the homeostatic mitochondrial transport system to both pre and post- synaptic terminals has been shown to cause synaptic loss, as the mitochondria are essential for $Ca+$ mechanics. Because $Ca2+$ is a fundamental signaling mechanism involved in many cellular physiological functions, subtle alterations of its homeostasis lead to profound functional change [30].

In addition to modulation of $Ca+$ movements through the neuronal cellular compartments, an increasing number of signaling functions for mitochondria have recently been unveiled. Slow and prolonged changes in mitochondrial potential exhibit both temporal and spatial correlations with the intensity of electrical activity in glutamate-receptor-mediated patterned synaptic activity. Additionally, impairment of mitochondrial transport into the presynaptic terminal has been shown to cause abnormal neurotransmission during intense stimulations, impaired presynaptic short-term plasticity, and accelerated synaptic depression under high-frequency firing. Therefore, it is possible that cognitive decline occurring with normal aging is not merely associated with significant neuronal loss, but is rather the result of changes in synaptic connectivity and loss of temporal regulation of homeostatic functions, that may include mitochondrial control of $Ca+$ [31].

When combining the molecular theories with those of both temporal and Hebbian methodologies behind the synapse, the once elusive dots become connected. The invoked mechanisms behind DTME/HAW as synaptopathies incorporates the importance of the temporal axis on the strength of synaptic interactions between neurons in the brain and the subsequent deregulation of homeostatic mechanisms, allowing a 4D clinical approach to synaptic dysplasticity. The Hebbian component of STDP implements the causal nature of Hebb's postulate: "cell A reliably contributes to spiking of postsynaptic cell B, the functional strength of the synapse from A to B is increased" [32]. The axiom "cells that fire together, close in time, wire together". In reverse, it is imperative to the hypothesis of this paper, because the deviant neurological function that occurs by virtue of synaptic deterioration leads to a deficit in synaptic function that may occur faster than its recovery, implying that inter-regional competition due to coupling between different neuronal dendritic regions leads to the potentiation of one population of synapses at the expense of another. Spike timing dependence originates in both molecular coincidence detection within classical LTP/LTD pathways (e.g., by NMDA receptors) and the temporal requirements for dendritic electrogenesis. Therefore, Hebbian theory suggests that the unique benefits of spike timing dependence, while only one of many factors that oversees the plasticity that influences synaptic activity, includes the incorporation of timing dependence, network stability, synaptic competition, sequence learning and prediction, all vital factors when analyzing the underlying mechanisms behind synaptic dysfunction.

In the brain, waves of electrical activity trace out distinct and moldable algorithmic patterns across the nervous tissue. While it is yet unclear the exact patterns and roles that these waves play, traveling waves are highly correlated with the fine-tuning of neural circuits, providing a good mechanism for mediating the refinement of synapses. The spatial scale of connectivity patterns is reliant on wave speed and STDP time constant, reinforcing the idea of the 4D component of synaptic activity. Patterns of temporal differences between spike times of a given input neuron and output neuron can determine the strength of the respective synapse according to the Hebbian STDP rule, cluing us into the possible disintegration of synapses via the mechanism of accelerated aging that seems to occur during DTME and HAW. Important connectivity patterns can be unveiled using the wave theory to create a receptive field, determining largely the optimized function of any given neuron. Disruptive patterns provide clues regarding the pathologies in the receptive field that can affect interneuronal relationships between synapses. The model described by Bennett et al. (2015) shows that the lateral interactions between synapses result directly from the timing dependence of STDP which is mapped onto the 4D conformation of neurological function via spatio-temporal correlations of traveling waves, declaring that waves can induce strong associations between any two input neurons irrespective of separation as long as they are correlated with a specific time lag ($\Delta x = v\Delta t$). Clinically, we can draw the conclusion that the temporal component of synaptic activity is imperative to correct functioning of the neural algorithm that would be anomalous if synapses dysfunction. The challenge moving forward will be to understand how these mechanisms work together to integrate homeostatic information and orchestrate stable cellular, synaptic, circuit, and systemic functions in the neural circuit.

The electrical activity that the nervous system uses to establish stable communication throughout the recurrent network that drives LTP at synapses in the forward direction and LTD in the reverse, creates directional connections that are tuned due to selective responses, spontaneous repeated sequences of motor patterning, and the ability of the body to predict future events from past stimuli. It has been suggested that stimulating activity may influence the rates of synaptic and neuronal degeneration, preservation, and integrity. During normal aging and in neurodegenerative conditions in which cognitive decline or progressive impairment of muscle function is associated with early signs of synaptic dysfunction [33–36]. Simultaneous rapid sequential activation of two synaptically connected neurons leads to associative

synaptic plasticity, or changes in the strength of synapses between them [25], driving the robust plasticity of neural maps.

The use and disuse of synapses are thought to influence progression of several neurodegenerative diseases in which synaptic degeneration is an early event. There is compelling evidence that some forms of synaptic remodeling or withdrawal are highly sensitive to activity. For instance, the rate of postnatal synapse elimination, a controlled process of presynaptic withdrawal that has been well characterized at developing neuromuscular junctions (NMJs) or following nerve regeneration in adults, is readily modifiable and strongly influenced by activity [37–39]. In an experiment conducted by Brown et al (2015) on the neuromuscular synapse reaction in various conditions on WldS mice, they concluded that intensive stimulation in vivo, complete nerve blockage in vivo and intensive stimulation ex vivo all reduced synaptic protection mediated by *WldS*gene expression, providing direct evidence that the rate of neuromuscular synaptic degeneration in response to axotomy is in fact sensitive to activity and that either complete disuse or sustained high-frequency stimulation can both cause motor nerve terminals to be become more vulnerable to triggers of degeneration. They suggested that prolonged and intensive synaptic activity accelerates synaptic degeneration and the mechanism is sensitive to Ca+. The Hebbian STDP component of the presented synaptopathy hypothesis provides a well shown mechanism behind transneuronal degeneration, influencing the temporal element of neuronal firing, causing the successive homeostatic and clinical decline.

The rates of synaptic and neuronal degeneration, which occur both during normal aging and in neurodegenerative conditions, contributes to cognitive decline or progressive impairment of muscle function. Enter the concept of neurologic functional reserve. In light of this hypothesis, then, the unanswered question of how many synapses need to be lost or dysfunctional to lead to the corresponding symptomatology. The synaptic pruning mechanisms that occur during development, which allow for synapse elimination during postnatal refinement of neural circuits, have been found to contribute to synapse loss in Alzheimer's disease, suggesting that the disuse of such circuits causes them to decrease or cease firing. Spires-Jones et al (2014) additionally state that impairment of mitochondrial transport to pre and postsynaptic terminals is thought to cause synapse loss and eventual dying-back of axons due to the essential roles of mitochondria in ATP production and Ca+ buffering, further supporting our hypothesis: that the final anatomic site for both DTME and HAW are the heterogeneous microdisconnections of the synaptic units.

Into the future

If this unifying hypothesis proves plausible, that the etiopathogenesis of DTME and HAW is at the synapses/synaptic units, then, the goal to prevent or retard these two conditions may be to sustain, temporize, slow-down the synaptic regressions, by passive and active synaptic stimulations.

Future clinical protocols that induce forward synaptic activations may slow down the involution that results from disuse. Such may be accomplished via techniques that include external magnetic, electrical, auditory, visual, chemical stimulations and multisensorial virtual reality – most likely several applied close in time.

Authors role's

AAJV: concepts generation, design, bibliographical research, analysis and synthesis, drafting and writing, final approval.

RJM: concepts generation, design, bibliographical research, analysis and synthesis, drafting and writing.

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Conflict of interest

None.

Appendix A. Supplementary data

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