Review

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Sleepless in Captivity: Insomnia Kills the Von Economo Neurons

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Abstract: Forensic hospitals throughout the country house individuals with severe mental illness and history of criminal violations. Insomnia affects 67.4% of hospitalized patients with chronic neuropsychiatric disorders, indicating that these conditions may hijack human somnogenic pathways. Conversely, somnolence is a common adverse effect of many antipsychotic drugs, further highlighting a common etiopathogenesis. The role of dysfunctional mitochondria in psychopathology is well-established, however, the association of these organelles with sleep physiology is novel. Indeed, reducing neuronal oxidative stress by importing mitochondria from astrocytes, may be the purpose of human slumber. This model may explain mitochondrial dysfunction during anesthesia as well as in the rare genetic disease, fatal familial insomnia. In this narrative review, we focus on the salience network of the brain, a common denominator for insomnia, neuropsychiatric and neurodegenerative disorders. We also discuss mitochondria-protecting strategies, including membrane lipid replacement, natural and synthetic phenazine and phenothiazine derivatives.

Keywords: Von Economo Neuron; interoceptive awareness; frontotemporal dementia behavioral variant; phenazines

Introduction

One of the most common sleep disorders in the United States, primary insomnia, is usually defined as long sleep latency, difficulty staying asleep, prolonged nighttime wakefulness, and/or early morning awakening [1]. In prison, approximately 60% of inmates experience insomnia, a prevalence 6-10 times higher than in the population at large [2]. Moreover, insomnia is present in 67.4% of hospitalized patients with severe mental illness, suggesting that the pathways of sleep and neuropathology are highly intertwined [3].

Forensic psychiatric hospitals admit patients with schizophrenia (SCZ) or schizophrenia-like disorders (SLDs) and criminal violations. Insomnia is common in this population and failure to address this condition may increase healthcare expenditure due to medical complications, including metabolic, cardiovascular, and neurodegenerative disorders. The salience network (SN), comprised of insular cortex (IC), anterior cingulate cortex (ACC) and several subcortical nodes, has recently been implicated in the etiopathogenesis of insomnia, SCZ, and neurodegenerative disorders [4–9]. Von Economo neurons (VENS), a special class of large, spindle-shaped cells found only in humans and superior mammals, are believed to drive empathy, social awareness, fairness, and alertness, connecting sleep with the higher brain functions [10,11]. VENS reside in the SN and play a key role in switching the attentional focus from interoception to exteroception as required by each situation.

At the molecular level, incarceration, insomnia, and severe mental illness have been associated with premature cellular senescence, a phenotype marked by increased intracellular iron and mitochondrial depletion [11–18]. Premature cellular senescence may be triggered by activating the master regulator of cellular aging, aryl hydrocarbon receptor (AhR), residing in both the cytosol and

mitochondria [19–21]. Senescent cells upregulate intracellular iron which in the proximity of cytosolic fats, increases the risk of lipid peroxidation and neuronal demise by ferroptosis [22–24]. Ferroptosis is a programmed, cell death induced by iron in the context of antioxidant failure marked by depletion of glutathione peroxidase-4 (GPX-4) [25,26]. GPX-4 is a mitochondrial enzyme which averts ferroptosis by repairing the oxidized phospholipids and cholesterol in mitochondrial and neuronal membranes [27].

Antipsychotic drugs are known for causing somnolence, indicating a likely interference with the human sleep pathways. For example, phenothiazines, induce sleep by antagonizing histamine H1 and alpha1 adrenergic receptors [28]. Clozapine, an AhR-activating ligand, may induce somnolence by altering the expression of circadian clock genes, some of which are controlled by the AhR [29,30]. Aside from clozapine, oxidized cell membrane lipids also bind AhR, possibly interfering with sleep physiology.

The phenothiazine class of antipsychotic drugs are potent inhibitors of cholesterol metabolism as they lower 7-dehydrocholesterol reductase (7DHC), upregulating 7-dehydrocholesterol (7DHC), a lipid which gets incorporated into the plasma and mitochondrial membranes, strengthening the lipid bilayer [31]. For example, trifluoperazine was shown to protect mitochondria by inhibiting membrane permeability and pore formation [32]. Moreover, phenothiazines intercalate themselves into the lipid bilayer of plasma and mitochondrial membranes, inhibiting peroxidation, thus, protecting the neurons from ferroptosis [33–35]. Interestingly, chlorpromazine was found effective against prion diseases, emphasizing a likely beneficial role in fatal familial insomnia (FFI) [36].

Dysfunctional mitochondria and impaired oxidative phosphorylation (OXPHOS), increases glycolysis and lactic acid levels, a metabolic pattern characteristic of SCZ or SLDs [37]. Indeed, increased lactate, considered a marker of sleep deprivation, likely activates mitochondrial AhR (mitoAhR), disrupting the organelle [38–40]. This is significant as lactate and neuro-metabolism likely comprise another sleep pathway hijacked by mental illness.

To compensate for dysfunctional mitochondria, neurons import these organelles from glial cells, especially the astrocyte [41,42]. In large cells, such as VENS, mitochondria are more vulnerable to damage and autophagic elimination as they undergo more wear and tear during their journey through the long axons of these neurons [43]. Due to their small number (around 193, 000) and their large sizes, VENS are more susceptible to plasma membrane oxidative stress, which may trigger significant pathology even after a limited neuronal loss, a pathology encountered in frontotemporal dementia behavioral variant (bvFTD).

Since mitochondria are crucial for neuronal function, preserving the integrity of these organelles via membrane lipid replacement (MLR) and other natural strategies, is of utmost importance. Microbial phenazines and the novel antioxidant phenothiazine derivatives, offer new opportunities to combat insomnia, psychosis, and neurodegeneration at the level of cell and mitochondrial membranes.

SN in sleep and neuropathology

The SN is comprised of anterior cingulate cortex (ACC) and anterior insular cortex (AIC) which along with subcortical nodes in the hypothalamus, thalamus, striatum, and midbrain process salient stimuli [44,45]. SN functions as a switch between exteroception and interoception or central executive network (CEN) and default mode network (DMN), depending on stimulus relevance [46]. Switching from CEN to DMN and vice versa is impaired in severe mental illness, insomnia, and neurodegenerative disorders [47]. Several antipsychotic drugs are known to lower the assignment of salience to objects and events, restoring the SN function, likely ameliorating both the psychotic symptoms and insomnia [48].

The SN harbors VENs, which are large, corkscrew neurons located in layer V of the IC and ACC. These non-telencephalic cells are believed to drive the prosocial cognition, empathy, and emotional intelligence. As parts of the SN, VENS respond to endogenous or exogenous stimuli in the order of priority. VENS are selectively eliminated in bvFTD, a disorder marked by criminal violations, lack of empathy, poor insight, and sleep impairment [49–53].

Under physiological circumstances, sleep is driven by the ventrolateral preoptic nucleus (VLPO) of the anterior hypothalamus which releases inhibitory neurotransmitters, including, γ-aminobutyric acid (GABA), and galanin [54]. The opposing system, orexin (hypocretin) neurons in the lateral hypothalamus, inhibit VLPO [55–57]. In addition, orexin/hypocretin neurons induce wakefulness by blocking the melanin concentrating hormone (MCH), a somnogen released by the hypothalamus and zona incerta [58,59]. Orexin and DA, the key players of saliency, have been implicated in the neuropsychiatric disorders associated with sleep disturbances, including narcolepsy, attention-deficit/hyperactivity disorder (ADHD), and Parkinson's disease (PD) [60]. Histamine is another wakefulness-promoting neurotransmitter implicated in SCZ and SLDs and a novel target for treating the negative and cognitive symptoms [61].

To better comprehend the pathogenesis of insomnia, it is necessary to study the pathways of wakefulness, a brain state driving self-awareness and probably consciousness [62]. Early studies on this subject have focused on the locus coeruleus, midbrain tegmentum, pons, and parabrachial nucleus, as neurons in these regions are active during wakefulness [63,64]. In the early 1900s, while studying encephalitis lethargica, Constantin von Economo found that lesions in the posterior hypothalamus were associated with sleep, hypothesizing that this area contained the "center of wakefulness" [65–67].

FFI, a rare autosomal dominant disease, is marked by hypometabolism and neuronal loss in the thalamus and cingulate cortex, linking this condition to the SN [68]. Indeed, dysfunctional salience perception in FFI is reflected in sleep disturbances, psychiatric disorders, and autonomic dysregulation, pathologies previously linked to AIC and ACC [69–72]. The role of SN in sleep physiology and pathology is further highlighted by the fact that anesthetics, especially propofol, lower salience processing, inducing sleep [68–78]. Moreover, recent studies on sleep deprived human volunteers and patients with primary insomnia demonstrated altered connectivity in AIC, further linking SN to sleep and wakefulness [79,80]. Furthermore, several preclinical studies are in line with the findings in humans, implicating the SN in slumber homeostasis [74,81].

Aside from insomnia and neuropsychiatric pathology, the SN connectivity is disrupted in neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and bvFTD, suggesting that insomnia and neuropathology are highly intertwined [82–86]. Indeed, dysfunctional AIC and ACC connectivity may account for the criminal violations in patients with bvFTD in which breaking the law may often be the initial dementia symptom [87,88].

bvFTD as a secondary psychopathy

The second most common neurodegenerative disorder after AD, bvFTD, is marked by inappropriate emotional responses and disinhibited behaviors, often leading to criminal violations [52,89]. In forensic institutions, individuals with first incarceration after the age 55 may suffer from bvFTD, an entity difficult to diagnose as memory may remain intact for longer periods of time. As a result, bvFTD is often missed or misdiagnosed as antisocial personality disorder (APD), SCZ, or SLDs [90].

Over the past two decades, the number of senior first offenders has grown in parallel with the prevalence of young-onset dementia (YOD)(emergence of symptoms before age 65), a subgroup of neurodegenerative disorders, which may include bvFTD [91,92]. Indeed, recent studies have revealed that the prevalence of bvFTD has increased from 15/100, 000 in 2013 to 119 per 100, 000 in 2021, mirroring the growing number of forensic detainees with this diagnosis [92,93].

Compared to AD in which 12% of patients exhibit criminal behavior, bvFTD is associated with a crime rate of 54%, suggesting an acquired psychopathy [94]. Frontotemporal lobar degeneration (FTLD), the pathology driving bvFTD, is believed to selectively eliminate the "honesty cells", VENS, predisposing to impulsivity and criminal violations [50,51]. Indeed, due to their large size, VENs may be particularly vulnerable to oxidative stress and mitochondrial depletion [95]. The latter is likely due to autophagy of damaged organelles traveling through the long VENS axons. Indeed, lysosomal aggregates, hallmarks of hyperactive autophagy, were demonstrated in VENS derived from patients with bvFTD and SCZ, suggesting excessive mitophagy [95–97]. Depletion of VENS has been

associated with lack of empathy, aggressive behavior, and criminal violations documented in bvFTD and severe mental illness [51,52]. For example, homicide or attempted homicide have been documented in bvFTD, indicating that criminal behavior and murder can sometimes be the earliest manifestation of this disorder [98,99]. Since VENS are only present in large mammals, including humans, great apes, macaques, cetaceans, and elephants, but not in rodents, these cells are difficult to study in vivo [10]. VENS are larger than pyramidal neurons and drive interoceptive awareness, the ability to detect and process internal cues, such as heartbeat, respiration and the overall visceral state [100,101]. VENS are components of the SN, a large neuronal assembly which responds to intrinsic or extrinsic stimuli, shifting attention from CEN to DMN and vice versa [102,103].

Recent transcriptomic studies found that VENS express monoaminergic proteins, including vesicular monoamine transporter 2 (VMAT2) and adrenergic receptor α-1A (ADRA1A), suggesting involvement in autonomic functions, including the circadian rhythm [104–106]. Indeed, impaired monoaminergic signaling has been documented in insomnia, bvFTD, SCZ, and SLDs, implicating VENS in these pathologies [107–111].
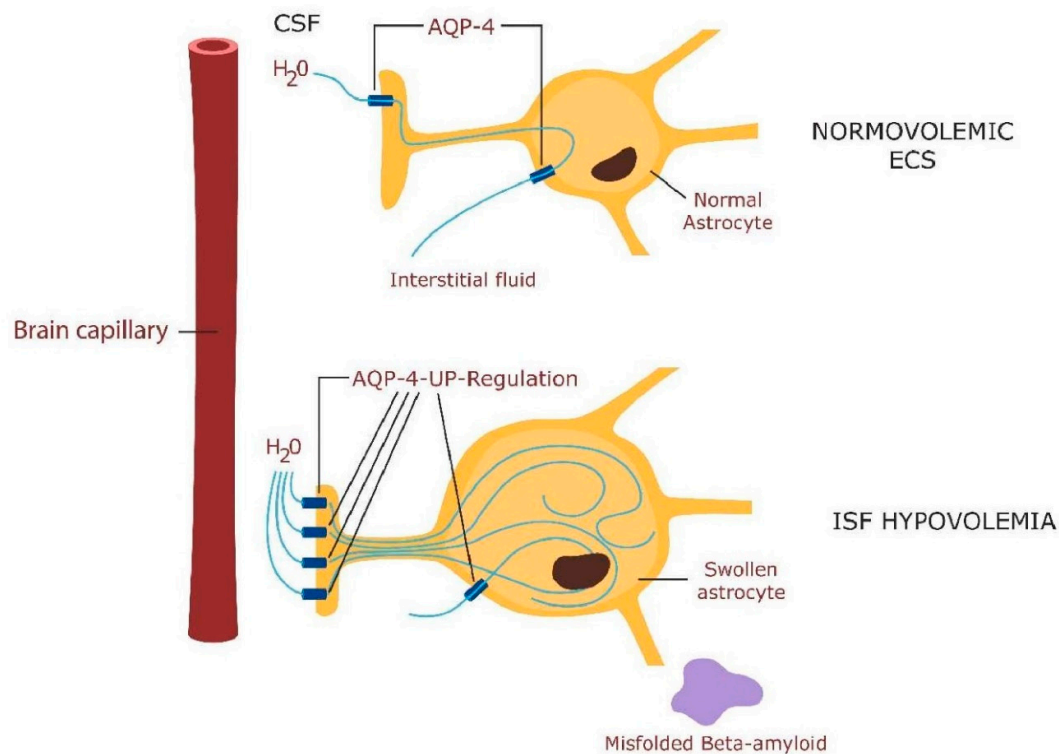
Sleep and glial cells

Astrocytes, the most numerous brain cells communicate with each other via calcium waves, attaining synchronization with neurons which supports the slow-wave sleep [112,113]. Moreover, astrocytes release somnogenic molecules, including adenosine, lactate, glutamate, GABA, and interleukin-1 (IL-1), which influence the status of neuronal cells, predisposing to sleep [114].

Astrocytes are central to the neurovascular unit (NVU) and bridge the gap between the neuron and brain microvessels, regulating the flow of interstitial fluid through the aquaporin 4 (AQP-4) receptors [115](Figure 1). The volume of the brain interstitial fluid (ISF) fluctuates in a circadian manner as it flows through the glymphatic system, a mechanism for clearing misfolded proteins during sleep [116]. The glymphatic system can also carry extracellular vesicles containing mitochondria from astrocytes to neurons [117]. Astrocytes support the neurons by generating GPX-4 to avert neuronal death by ferroptosis. GPX-4 functions to repair oxidized lipids and oxysterols, including 7-ketocholesterol (7KCl), toxins that disrupt plasma and mitochondrial membranes, triggering neuronal death [118]. As mitochondria play a key role in sleep homeostasis, insomnia may be the result of plasma or mitochondrial membrane oxidation [119]. Indeed, it has been suggested that sleep is necessary for abrogating neuronal oxidative stress [120].

Intracellular iron is stored in ferritin and released for intracellular needs via ferritinophagy (ferritin autophagy) in lysosomes. Several antipsychotic drugs, including haloperidol, accumulate in lysosomes disrupting ferritinophagy, which in return lowers intracellular iron, averting ferroptosis [121,122] (Figure 2). This may highlight a DA-independent, antipsychotic action of haloperidol, suggesting that dopaminergic blockade is not the only psychosis-deterring mechanism of this drug. Indeed, ferroptosis of hippocampal neurons, documented in AD and severe mental illness, is the likely cause of cognitive impairment and negative symptoms in these conditions [123,124]. Prolonged insomnia was demonstrated to damage the astrocyte which in return may trigger neuronal demise [125]. Moreover, chronic sleep loss was demonstrated to activate both astrocytes and microglia, turning these cells into neurotoxic phenotypes capable of eliminating healthy neurons and synapses [126–128].

Figure 1. Astrocytes contact cerebral microvessels with their end-feet processes, delineating a pathway for the flow of extracellular fluid, known as the glymphatic system. The volume of interstitial fluid (ISF) in the brain parenchyma varies with the brain work. During high intensity work, AQP-4 water receptors are upregulated in the end-feet, pumping the ISF into astrocytes. This results in low ISF (hypovolemia). During sleep (low intensity brain work), less ISF enters the astrocyte. The circulation of ISF clears the molecular debris (including beta amyloid) from the extracellular space.
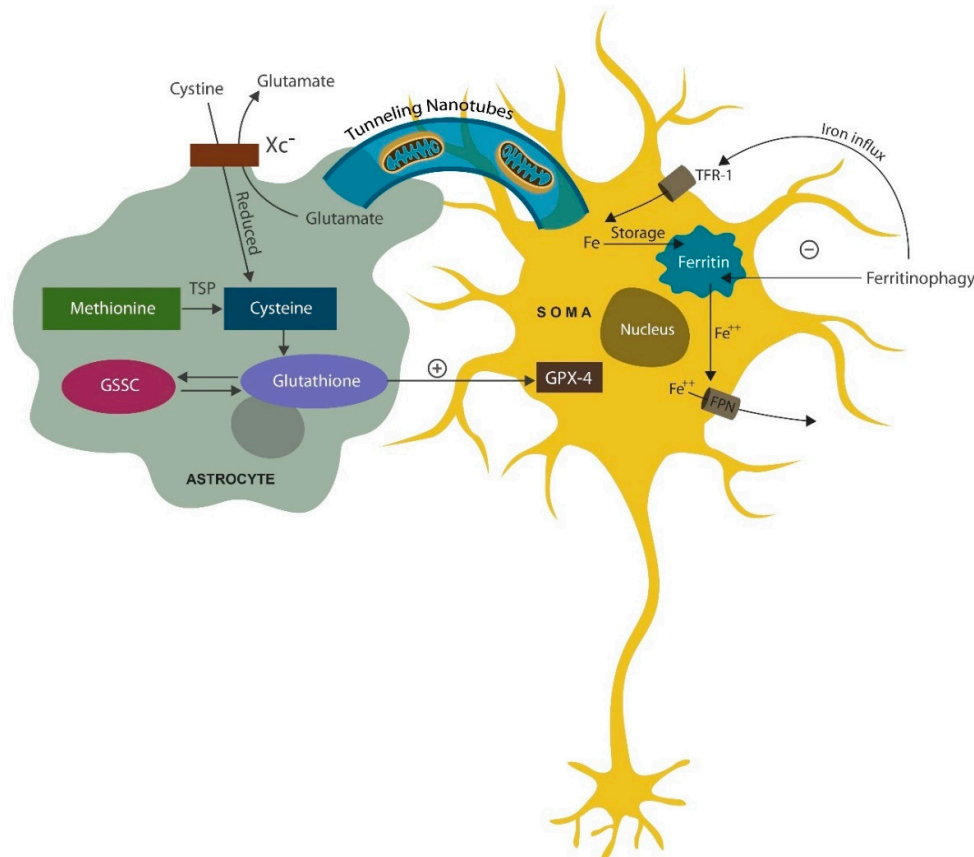
Mitochondria and aryl hydrocarbon receptor

Recent studies have implicated mitochondria in the pathophysiology of sleep and neurodegenerative disorders, while the role of these organelles in severe mental illness, including SCZ and SLDs, has been previously established [129,130]. Lipid peroxidation of mitochondrial membrane and iron upregulation can trigger ferroptosis and organelle demise [131–134]. Indeed, lipid peroxides and oxysterols, such as 7KCl, are mitoAhR ligands, contributing to mitochondrial dysfunction and autophagic elimination [135]. AhR is a xenobiotic sensor which regulates cytochrome p450 and binds the environmental toxin, dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin). Other AhR ligands, include somnogens, such as phenazines, melatonin, and tryptophan derivatives, which participate in the physiology of sleep, wakefulness, and the circadian rhythm [136–138]. In addition, reactive oxygen species (ROS), known to induce sleep via a redox-sensitive potassium channel, are AhR ligands, bringing this transcription factor in the arena of slumber, mental illness, and neurodegeneration [131,139]. Indeed, microbial phenazines, including pyocyanin and 1-hydroxyphenazine, activate AhR, influencing the transcription of many genes, including those involved in sleep regulation [140,141].

The importance of mitochondria in sleep physiology is further substantiated by the organelle involvement in FFI as well as in general anesthesia [142,143]. Indeed, general anesthetics are known to inhibit N-methyl-d-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors, while stimulating GABA. NMDA and AMPA upregulate intracellular and mitochondrial calcium, inducing cell and organelle demise [144]. Interestingly, elevated mitochondrial calcium, a characteristic of prion diseases, may link these organelles to FFI [145,146]. Indeed, the prion peptide causes calcium inflow via L-type calcium channels, triggering neuronal damage and apoptosis [147]. In contrast, the typical antipsychotic, chlorpromazine, not only induces sleep, but also exerts anti-prion properties, probably by promoting autophagy of the misfolded protein [148–150].

Mitochondrial trafficking from astrocytes to neurons, supports neuronal bioenergetic needs, especially in large pyramidal cells or VENs. Mitochondria can be imported via cell-cell fusion, tunneling nanotubes (cytoskeletal protrusions reaching to other cells) as well as transported by extracellular vesicles [151,152] (Figure 2). Moreover, astrocytes generate GPX-4 from cysteine obtained via the cystine/glutamate antiporter system (Xc−) or by transmethylation of methionine. Glutathione is generated from cysteine and glutathione disulfide (GSSC) [153] (Figure 2).

Mitochondrial trafficking as well as autophagy (mitophagy) occur during sleep, probably explaining the reason most living beings require rest [154]. Interestingly, serotonin (5-HT) promotes mitochondrial transport in hippocampal neurons, suggesting that antidepressant drugs, serotonin reuptake inhibitors (SSRIs), may "exert their action by supplying healthy mitochondria to stressed neurons [155]. This may imply that ROS accumulation during wakefulness may induce slumber to repair oxidized lipids and import mitochondria from glial cells [120,131,139]. In addition, accumulation of intracellular microtubule-associated protein tau (MAPT) in VENS likely impairs mitochondrial transport, contributing to bvFTD pathogenesis [156].

Figure 2. Astrocytes support the postmitotic, long-lived, neurons by helping them avert death by ferroptosis and loss of mitochondria. The former is accomplished by exporting GPX-4 to neurons (to repair oxidized lipids), while the latter by exporting healthy mitochondria to neuronal cells (via tunneling nanotubules, extracellular vesicles, or cell-cell fusion). Astrocytes import cystine via cystine/glutamate antiporter (Xc-). Cystine is reduced to cysteine and generates glutathione and GPX-4 (which is transferred to neurons). Cysteine can also be derived from methionine, while glutathione can be generated from cysteine and glutathione disulfide (GSSC). In neurons, iron is stored in ferritin and when needed, ferritin undergoes ferritinophagy (autophagy) in lysosomes, releasing free iron. Iron ingresses the neuron via transferrin receptor 1 (TRF-1), while the excess intracellular iron is eliminated via ferroportin.

Four cases of bvFTD from our hospital and the community

Case #1 **The teacher who shot her neighbor**

Ms. KS (initials changed), a Caucasian female, age 68, divorced, retired elementary school teacher, lived alone prior to her admission to Patton State Hospital. Ms. KS did not have a psychiatric history until the age of 56 when she purchased a gun and shot her neighbor in the shoulder. She stated that she attacked the man because he was spying on her and intruded into her house during the night. She was convicted of attempted murder and sent to prison, where her condition deteriorated, prompting transfer to our forensic institution. KS was diagnosed with SCZ and admitted as a forensic detainee.

During her hospital stay, KS was treated with various antipsychotic drugs with minimal symptomatic relief. She was unaware that she did anything wrong and her poor insight and impulsivity were documented during her six years of hospital stay. Because of poor insight, KS never met criteria for the conditional release program (CONREP).

In 2014, KS became more forgetful, required assistance with most activities of daily living (ADLs), and exhibited a change in her dietary preferences. For example, she asked for ice cream daily, although earlier in her life she detested ice cream. In time, KS became more apathetic and often refused to get out of bed.   The internal medicine consultant performed a dementia workup, but the laboratory studies came back normal, except for mild anemia, and a vitamin D level of 29.3 nmol/L. KS scored 25/30 on Mini Mental Status Exam (MMSE) and when a Montreal Cognitive Assessment (MoCA) was administered, the score was 23/30, consistent with executive dysfunction. Neuropsychology consult was called, and after a battery of tests, bvFTD was diagnosed.

With this information, the treatment team petitioned the Court, arguing that KS did not benefit from hospitalization in a forensic institution as she was not expected to recover. The judge agreed with the treating clinicians and ordered placement in a facility specialized in dementia.

Due to the numerous clinical and legal ramifications (discussed below), this case was featured in the mass media at the time:

https://www.reuters.com/article/us-crime-dementia-idUSKBN0KE1Q020150105/

https://www.foxnews.com/health/breaking-the-law-may-be-a-sign-of-dementia

https://clbb.mgh.harvard.edu/when-frontotemporal-dementia-leads-to-crime-prosecution-or-protection/

Case #2 **The attorney with a sweet tooth**

An outpatient we treated in 2013, was a 72 years old, retired attorney, arrested because he stole chocolate from a grocery store while casually conversing with the owner. When confronted, he replied: "what's the problem, I have a sweet tooth".   According to the family, the patient came across as careless and indifferent of his children and the spouse, being either apathetic or angry and irritable. For example, when he learned that his son-in-law died unexpectedly, he responded by saying "let's go out to eat". His eating habits had changed dramatically, according to his wife, consuming mostly sweets which previously he had avoided.   When told to eat more nutritious food, he often became angry.

Case #3 **The psychiatrist turned a drug dealer**

Dr. Joel Stanley Dreyer was a well-respected psychiatrist who practiced in Riverside, California. In 1990s, Dr. Dreyer was diagnosed with bvFTD but continued to practice psychiatry, and in 2010 was convicted for prescribing, selling, and distributing large amounts of addictive painkillers. As a result of careless prescribing, one person died of an overdose and Dr. Dreyer was convicted and served ten years in prison despite having been diagnosed with bvFTD prior to his crime. This case emphasizes that some jurisdictions do not recognize bvFTD as an attenuating circumstance. The court ruling was based on the testimony of the prison psychiatrist who did not challenge the diagnosis of bvFTD but stated that since not all individuals with this disorder engage in criminal behavior, "direct causality" between Dr. Dreyer's crime and bvFTD could not be established.   A detailed history of this case can be found at the link below:

https://story.californiasunday.com/joel-dreyer-criminal-psychiatrist/.

Case #4 **The Buick murderer**

On July 16, 2003, Mr. GRW, an 83 years old man crashed his Buick LeSabre in an open-air market in Santa Monica, California, killing 10 and injuring 63 individuals. Despite the catastrophic event he caused, GRW did not express remorse, showed indifference, callousness, and lack of empathy. In the court, he appeared apathetic, angry, and unapologetic, stating that he was sorry the dead and injured could not "enjoy the value of their purchases".   No psychiatric evaluation was ordered because there was no previous history, however, criminal behavior may often represent the first symptom of bvFTD. Despite never being diagnosed with a neurodegenerative disorder, people who knew GRW noticed a drastic personality change in the years prior to this event, indicative of bvFTD. His neighbors, friends, and his pastor, described GRW as caring, pleasant, and friendly individual. He had been married for over 60 years, was compassionate, involved in peoples' lives, and after retirement, volunteered with various civic organizations. Although GRW was never officially diagnosed with bvFTD, this case illustrates the difficulty clinicians encounter because this neurodegenerative disorder affects the executive function, leaving memory intact for many years. Indeed, shortly before his crime, GRW was able to pass his DMV license renewal test, suggesting that his memory was unaffected. Since in California drivers who are 70 or older must renew their driver's license in person, GRW did not raise a dementia red flag with the DMV worker.

Discussion

Since bvFTD comprises 2.7% of all dementias and in early stages, patients retain their cognitive abilities, this condition is often misdiagnosed as SCZ, depression, or bipolar disorder, and frequently admitted to psychiatric institutions.   Patients with bvFTD respond poorly to antipsychotic drugs, are often labeled "treatment resistant", and prescribed additional psychotropics [157]. Moreover, as criminal behavior is frequently the initial manifestation of bvFTD, clinicians rarely suspect this condition when examining an incarcerated individual. However, there are several characteristics of this disorder which should prompt the clinician to think of a neurodegenerative condition. These include absence of psychiatric history at a younger age, first legal violation after the age of 55, poor insight despite a previously successful life, sudden change in eating habits, altered sleep pattern, lack of empathy, and engaging in criminal acts despite the presence of witnesses.

Mitochondria-protective treatments

The key role of mitochondria in sleep disorders, SCZ, SLDs, and neurodegeneration, highlights the importance of mitoprotective approaches to resuscitate, replace, or increase the import of mitochondria from glial cells. For example, treatment with SSRIs during the early stages of dementias, may delay the onset of cognitive decline. Along this line, a recent study found that treatment with SSRIs slowed the conversion of mild cognitive impairment to frank dementia, suggesting that prophylactic treatment with these agents may be beneficial [158]. In addition, natural anti-ferroptosis drugs and iron chelators, such as halogenated phenazines, may improve the course of neurodegenerative disorders, suggesting novel therapeutic strategies [159,160].

Membrane Lipid Replacement (MLR)

MLR refers to the oral supplementation with natural, cell membrane glycerophospholipids and kaempferol (3,4′,5,7-tetrahydroxyflavone), a natural flavonoid found in tea, broccoli, cabbage, kale, beans, endive, leek, tomato, strawberries, and grapes [161]. Kaempferol is a glycogen synthase kinase-3β (GSK-3β) inhibitor which prevents sleep deprivation-induced cognitive decline [162,163]. Like lithium and several antipsychotic drugs, kaempferol blocks GSK-3β, an enzyme previously implicated in SCZ and circadian rhythm disorders, suggesting that this natural compound may exert antipsychotic properties without the adverse effects of conventional therapeutics [164–167].

The aim of MLR + kaempferol is gradual replacement of damaged phospholipids and oxysterols from neuronal and/or mitochondrial membranes with natural glycerophospholipids and a polyphenol. Indeed, oxidized membrane lipids have been implicated in SCZ, SLDs, insomnia, and neurodegeneration, while MLR and kaempferol offer a dual mechanism of action: 1) elimination of lipid peroxides and 2) GSK-3β inhibition [168]. Replacing oxidized plasma and/or mitochondrial membrane fats with healthy natural lipids, averts deformation of neuronal membrane and misalignment of neuroreceptors. Conversely, oxidized membrane lipids and ferroptosis alter the biophysical properties of membranes, disrupting neuronal functions [169].
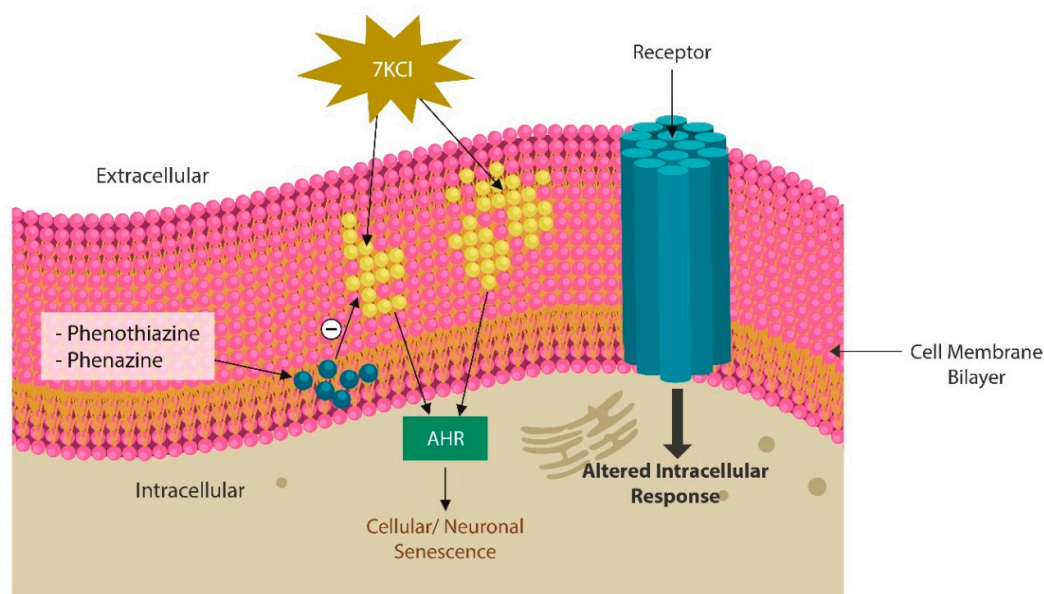
Phenazines and phenothiazine derivatives

Phenazines are nitrogen-containing heterocyclic compounds produced by various marine and terrestrial microorganisms which participate in microbial clearance, iron signaling, and biofilm formation [170]. Phenazines can be natural (bacteria-derived) or synthetic.

Natural phenazines, such as iodinin (1.6-dihydroxy-N5, N10-dioxide phenazine) and myxin, are antibiotics which have been known for several decades [171]. The newer, terpenoid, glycosylated and fused phenazines, are derived from various *Streptomyces* species and exert antibiotic and anticancer effects. For example, geranylphenazinediol is an inhibitor of human acetylcholinesterase with potential benefit in neurodegenerative disorders without the adverse effects of the manufactured drugs [172]. Other natural phenazines, including baraphenazines, leucanicidin and endophenasides, exert antimicrobial, anticancer activity, and very likely possess antipsychotic properties [173–175].
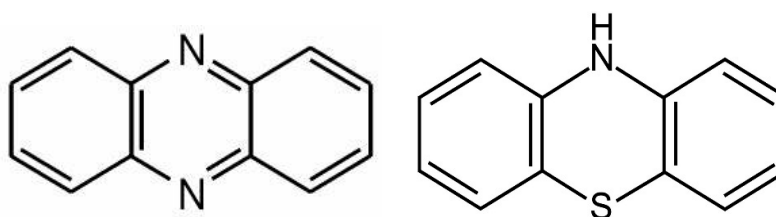
Synthetic phenazine derivatives consist of over 6,000 compounds, exerting antimicrobial, antiparasitic, neuroprotective, anti-inflammatory, and anticancer activities [176–178]. To the best of our knowledge, natural or synthetic phenazines have not been tested for SCZ, insomnia, or neurodegeneration. Pontemazines A and B are neuroprotective phenazine derivatives which in animal studies have rescued hippocampal neurons from glutamate cytotoxicity, highlighting their pro-cognitive properties which could benefit patients with negative symptoms of SCZ or neurodegenerative disorders [176].

Synthetic phenazines exert antioxidant and radical-scavenging properties, inhibit lipid peroxidation, suggesting beneficial effects in severe insomnia, mental illness and neurodegeneration [179,180](Figure 3). Moreover, halogenated phenazines act as iron chelators, likely preventing neuronal ferroptosis [181]. We believe that Pontemazines and halogenated phenazines should be assessed for antipsychotic/anti-neurodegenerative properties.

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Figure 3. The lipid bilayer of neuronal membrane is easily oxidated when intracellular iron is upregulated. Oxysterols, including 7-Ketocholesterol (a toxic oxide), and oxidated phospholipids alter the biophysical properties of cell membranes, disrupting neurotransmission. In addition, oxidized lipids activate AhR, triggering premature neuronal senescence.   Phenazines, Phenothiazines, and their derivatives, intercalate themselves into the lipid bilayer, repairing the lipids in cellular and/or mitochondrial membranes.

From the biochemical standpoint, phenazines are almost identical to phenothiazine antipsychotics and likely possess similar properties (Figure 4). Phenothiazines are typical antipsychotic drugs utilized primarily for SCZ and SLDs which block dopaminergic transmission at the level of postsynaptic neuron. Several phenothiazines influence other receptors, including adrenergic, histaminergic, and cholinergic, exerting various clinical effects as well as adverse reactions. Aside from psychotic disorders, phenothiazines are also used for the treatment of migraine headaches, hiccups, nausea, vomiting, and cancer [182]. Like phenazines, phenothiazines intercalate themselves into the lipid bilayer of plasma and mitochondrial membranes, disrupting the curvature and receptor alignment on neuronal/mitochondrial surfaces [183](Figure 3). In contrast, oxidized lipids, including 7-ketocholesterol (7KCl), form looped structures, generating membrane curvatures and pores, that may trigger cell death [184].

Figure 4. Phenazine vs. Phenothiazine: similarities and differences.

Antioxidant phenothiazine and their derivatives have recently been developed for cancer, cardiovascular disease (CVD), *Mycobacterium leprae* and other antibiotic-resistant microbes [185,186].

Phenothiazine derivatives exert anti-peroxidation properties and protect against lipid pathology and ferroptosis, suggesting efficacy as antipsychotic drugs [187]. In addition, antioxidant phenothiazines are likely beneficial for insomnia and neurodegenerative disorders, suggesting that these compounds should be tested for neuropsychiatric pathology [186].

Propenylphenothiazine is a potent antioxidant with electron-donor capability that could prevent gray matter loss, a hallmark of SCZ and SLDs [188,189]. Electron-donating psychotropic drugs have been known to preserve the brain volume, suggesting that propenylphenothiazine may treat psychosis, without reducing the gray matter volume. The majority of conventional antipsychotic drugs are electron-acceptors which often lower the brain volume as documented by many neuroimaging studies [190–193]. An even newer category of tetracyclic and pentacyclic phenothiazines with antioxidant properties have recently been developed, suggesting likely efficacy for cognitive impairment and negative SCZ symptoms [194]. Moreover, the N10-carbonyl-substituted phenothiazines were demonstrated to inhibit lipid peroxidation, suggesting superior antipsychotic efficacy [187].

Mitochondrial transfer and transplantation

The early studies on mitochondrial transplantation, from the 1980s, utilized co-incubation of various cell types with naked mitochondria, hoping that cells would internalize the organelles from the extracellular environment [195]. Later, HeLa cells and mesenchymal stem cells were used as mitochondrial sources and found that successful organelle uptake occurred in a short time interval of 1-2 hours [196–198]. At present, mitochondrial transplantation into cardiomyocytes has been accomplished successfully and confirmed by mitochondrial DNA (mtDNA) detected in host cells [199,200].

Mitochondrial transplantation and neuronal rescue from ferroptosis have been performed successfully in both animals and humans, suggesting a novel strategy for neurometabolic disorders [201]. To our knowledge, mitochondrial transplantation has not been attempted in sleep disorders, while in mental illness, it has been tried in animal models only [132]. Trafficking mitochondria from astrocytes and microglia to neurons can take place spontaneously after brain injuries, reflecting a likely compensatory mechanism to preserve neuronal viability [202]. In addition, it has been established that SSRIs, GJA1-20K, and CD38 signaling can facilitate mitochondrial transfer, emphasizing potential strategies for insomnia, severe mental illness, and neurodegeneration [203,204].

Conclusions

Forensic institutions throughout the country house individuals with severe mental illness and often comorbid insomnia, suggesting overlapping pathogeneses. Loss of neurons due to impaired sleep along with SCZ or SLDs-related gray matter depletion, may trigger the premature development of dementias and other medical complications. These comorbidities increase healthcare expenditures and shorten patients' lifespan, therefore, identifying and treating these conditions early is essential.

YOD, a category of neurodegenerative disorders which include bvFTD, has been on the rise over the past few decades as evidenced by the increased number of first offenders younger than 65. Selective loss of VENS in bvFTD is likely due to the large size of these cells, predisposing to peroxidation of plasma membrane lipids and mitochondrial loss by autophagy.

At the molecular level, AhR is the equivalent of cerebral VENS, as this protein responds to both endogenous and exogenous ligands, including the lipid peroxides and other insomnia and psychosis-related molecules.

Novel AhR ligands, phenazine and phenothiazine derivatives, as well as mitochondrial transfer or transplantation are potential new strategies for treating psychosis, insomnia, and neurodegeneration without additional loss of brain volume.

References

1. Sateia MJ, Doghramji K, Hauri PJ, Morin CM. Evaluation of chronic insomnia. An American Academy of Sleep Medicine review. Sleep. 2000;23:243–308.

2. Lindsay H Dewa, Bethan Thibaut, Natalie Pattison, Sean James Campbell, Thomas Woodcock, Paul Aylin, Stephanie Archer, Treating insomnia in people who are incarcerated: a feasibility study of a multi-component treatment pathway, SLEEP Advances, 2024;, zpae003, https://doi.org/10.1093/sleepadvances/zpae003

3. Talih F, Ajaltouni J, Ghandour H, Abu-Mohammad AS, Kobeissy F. Insomnia in hospitalized psychiatric patients: prevalence and associated factors. Neuropsychiatr Dis Treat. 2018 Apr 10;14:969-975. doi: 10.2147/NDT.S160742.

4. Wang Y, Li M, Li W, Xiao L, Huo X, Ding J, Sun T. Is the insula linked to sleep? A systematic review and narrative synthesis. Heliyon. 2022 Nov 5;8(11):e11406. doi: 10.1016/j.heliyon.2022.e11406. PMID: 36387567; PMCID: PMC9647461

5. Li C, Dong M, Yin Y, Hua K, Fu S, Jiang G. Aberrant Effective Connectivity of the Right Anterior Insula in Primary Insomnia. Front Neurol. 2018 May 8;9:317. doi: 10.3389/fneur.2018.00317. PMID: 29867727; PMCID: PMC5951943.

6. Wylie KP, Tregellas JR. The role of the insula in schizophrenia. Schizophr Res. 2010 Nov;123(2-3):93-104. doi: 10.1016/j.schres.2010.08.027.

7. Fathy, Y.Y., Hoogers, S.E., Berendse, H.W. et al. Differential insular cortex sub-regional atrophy in neurodegenerative diseases: a systematic review and meta-analysis. Brain Imaging and Behavior 14, 2799–2816 (2020). https://doi.org/10.1007/s11682-019-00099-3

8. Koutsouleris N, Pantelis C, Velakoulis D, McGuire P, Dwyer DB, Urquijo-Castro MF, Paul R, Dong S, Popovic D, Oeztuerk O, Kambeitz J, et al. Exploring Links Between Psychosis and Frontotemporal Dementia Using Multimodal Machine Learning: Dementia Praecox Revisited. JAMA Psychiatry. 2022 Sep 1;79(9):907-919. doi: 10.1001/jamapsychiatry.2022.2075.

9. Triarhou LC. The percipient observations of Constantin von Economo on encephalitis lethargica and sleep disruption and their lasting impact on contemporary sleep research. Brain Res Bull. 2006 Apr 14;69(3):244-58. doi: 10.1016/j.brainresbull.2006.02.002. Epub 2006 Mar 3. PMID: 16564419.

10. Allman JM, Tetreault NA, Hakeem AY, Manaye KF, Semendeferi K, Erwin JM, Park S, Goubert V, Hof PR. The von Economo neurons in frontoinsular and anterior cingulate cortex in great apes and humans. Brain Struct Funct. 2010 Jun;214(5-6):495-517. doi: 10.1007/s00429-010-0254-0.

11. Berg MT, Rogers EM, Lei MK, Simons RL. Losing Years Doing Time: Incarceration Exposure and Accelerated Biological Aging among African American Adults. J Health Soc Behav. 2021 Dec;62(4):460-476. doi: 10.1177/00221465211052568.

12. Kaiksow FA, Brown L, Merss KB. Caring for the Rapidly Aging Incarcerated Population: The Role of Policy. J Gerontol Nurs. 2023 Mar;49(3):7-11. doi: 10.3928/00989134-20230209-02.

13. Papanastasiou E, Gaughran F, Smith S. Schizophrenia as segmental progeria. J R Soc Med. 2011 Nov;104(11):475-84. doi: 10.1258/jrsm.2011.110051.

14. Killilea DW, Wong SL, Cahaya HS, Atamna H, Ames BN. Iron accumulation during cellular senescence. Ann N Y Acad Sci. 2004 Jun;1019:365-7. doi: 10.1196/annals.1297.063.

15. Urrutia PJ, Mena NP, Núñez MT. The interplay between iron accumulation, mitochondrial dysfunction, and inflammation during the execution step of neurodegenerative disorders. Front Pharmacol. 2014 Mar 10;5:38. doi: 10.3389/fphar.2014.00038. PMID: 24653700; PMCID: PMC3948003.

16. Carvalhas-Almeida C, Cavadas C, Álvaro AR. The impact of insomnia on frailty and the hallmarks of aging. Aging Clin Exp Res. 2023 Feb;35(2):253-269. doi: 10.1007/s40520-022-02310-w.

17. Carroll JE, Prather AA. Sleep and Biological Aging: A Short Review. Curr Opin Endocr Metab Res. 2021 Jun;18:159-164. doi: 10.1016/j.coemr.2021.03.021

18. Skonieczna-Żydecka K, Jamioł-Milc D, Borecki K, Stachowska E, Zabielska P, Kamińska M, Karakiewicz B. The Prevalence of Insomnia and the Link between Iron Metabolism Genes Polymorphisms, TF rs1049296 C>T, TF rs3811647 G>A, TFR rs7385804 A>C, HAMP rs10421768 A>G and Sleep Disorders in Polish Individuals with ASD. Int J Environ Res Public Health. 2020 Jan 8;17(2):400. doi: 10.3390/ijerph17020400.

19. Nacarino-Palma A, Rico-Leo EM, Campisi J, Ramanathan A, González-Rico FJ, Rejano-Gordillo CM, Ordiales-Talavero A, Merino JM, Fernández-Salguero PM. Aryl hydrocarbon receptor blocks aging-induced senescence in the liver and fibroblast cells. Aging (Albany NY). 2022 May 26;14(10):4281-4304. doi: 10.18632/aging.204103.

20. Panda SK, Peng V, Sudan R, Ulezko Antonova A, Di Luccia B, Ohara TE, Fachi JL, Grajales-Reyes GE, Jaeger N, Trsan T, Gilfillan S, Cella M, Colonna M. Repression of the aryl-hydrocarbon receptor prevents oxidative stress and ferroptosis of intestinal intraepithelial lymphocytes. Immunity. 2023 Apr 11;56(4):797-812.e4. doi: 10.1016/j.immuni.2023.01.023.

21. Hwang HJ, Dornbos P, Steidemann M, Dunivin TK, Rizzo M, LaPres JJ. Mitochondrial-targeted aryl hydrocarbon receptor and the impact of 2,3,7,8-tetrachlorodibenzo-p-dioxin on cellular respiration and the mitochondrial proteome. Toxicol Appl Pharmacol. 2016 Aug 1;304:121-32. doi: 10.1016/j.taap.2016.04.005.

22. Dietrich-Muszalska A, Kontek B. Lipid peroxidation in patients with schizophrenia. Psychiatry Clin Neurosci. 2010 Oct;64(5):469-75. doi: 10.1111/j.1440-1819.2010.02132.x. PMID: 20923426.

23. Feng S, Chen J, Qu C, Yang L, Wu X, Wang S, Yang T, Liu H, Fang Y, Sun P. Identification of Ferroptosis-Related Genes in Schizophrenia Based on Bioinformatic Analysis. Genes (Basel). 2022 Nov 20;13(11):2168. doi: 10.3390/genes13112168.

24. Gulec M, Ozkol H, Selvi Y, Tuluce Y, Aydin A, Besiroglu L, Ozdemir PG. Oxidative stress in patients with primary insomnia. Prog Neuropsychopharmacol Biol Psychiatry. 2012 Jun 1;37(2):247-51. doi: 10.1016/j.pnpbp.2012.02.011.

25. Liang H, Van Remmen H, Frohlich V, Lechleiter J, Richardson A, Ran Q. Gpx4 protects mitochondrial ATP generation against oxidative damage. Biochem Biophys Res Commun. 2007 May 18;356(4):893-8. doi: 10.1016/j.bbrc.2007.03.045.

26. Seibt TM, Proneth B, Conrad M. Role of GPX4 in ferroptosis and its pharmacological implication. Free Radic Biol Med. 2019 Mar;133:144-152. doi: 10.1016/j.freeradbiomed.2018.09.014. Epub 2018 Sep 13. PMID: 30219704.

27. Cole-Ezea P, Swan D, Shanley D, Hesketh J. Glutathione peroxidase 4 has a major role in protecting mitochondria from oxidative damage and maintaining oxidative phosphorylation complexes in gut epithelial cells. Free Radic Biol Med. 2012 Aug 1;53(3):488-97. doi: 10.1016/j.freeradbiomed.2012.05.029

28. Fujii R, Hasuo H, Sakuma H, Okada M, Uchitani K. The efficacy and safety of intravenous chlorpromazine treatment for sleep disturbance in patients with incurable cancer, with oral administration difficulty: a 1-week, prospective observational study. Ann Palliat Med. 2021 Aug;10(8):8547-8556. doi: 10.21037/apm-21-948.

29. Tischkau SA. Mechanisms of circadian clock interactions with aryl hydrocarbon receptor signalling. Eur J Neurosci. 2020 Jan;51(1):379-395. doi: 10.1111/ejn.14361. Epub 2019 Feb 25.

30. Fehsel K, Schwanke K, Kappel BA, Fahimi E, Meisenzahl-Lechner E, Esser C, Hemmrich K, Haarmann-Stemmann T, Kojda G, Lange-Asschenfeldt C. Activation of the aryl hydrocarbon receptor by clozapine induces preadipocyte differentiation and contributes to endothelial dysfunction. J Psychopharmacol. 2022 Feb;36(2):191-201. doi: 10.1177/02698811211055811.

31. Korade Ž, Liu W, Warren EB, Armstrong K, Porter NA, Konradi C. Effect of psychotropic drug treatment on sterol metabolism. Schizophr Res. 2017 Sep;187:74-81. doi: 10.1016/j.schres.2017.02.001.

32. Kiani A, Nik SH, Khodadoost A, Salimi A, Pourahmad J. Trifluoperazine an Antipsychotic Drug and Inhibitor of Mitochondrial Permeability Transition Protects Cytarabine and Ifosfamide-Induced Neurotoxicity. Drug Res (Stuttg). 2020 Jun;70(6):265-272. doi: 10.1055/a-1154-8672

33. Roy D, Pathak DN, Singh R. Effects of chlorpromazine on the activities of antioxidant enzymes and lipid peroxidation in the various regions of aging rat brain. J Neurochem. 1984 Mar;42(3):628-33. doi: 10.1111/j.1471-4159.1984.tb02728.x.

34. Ficarra S, Russo A, Barreca D, Giunta E, Galtieri A, Tellone E. Short-Term Effects of Chlorpromazine on Oxidative Stress in Erythrocyte Functionality: Activation of Metabolism and Membrane Perturbation. Oxid Med Cell Longev. 2016;2016:2394130. doi: 10.1155/2016/2394130.

35. Chen JY, Brunauer LS, Chu FC, Helsel CM, Gedde MM, Huestis WH. Selective amphipathic nature of chlorpromazine binding to plasma membrane bilayers. Biochim Biophys Acta. 2003 Sep 22;1616(1):95-105. doi: 10.1016/s0005-2736(03)00229-3

36. Korth C, May BC, Cohen FE, Prusiner SB. Acridine and phenothiazine derivatives as pharmacotherapeutics for prion disease. Proc Natl Acad Sci U S A. 2001 Aug 14;98(17):9836-41. doi: 10.1073/pnas.161274798.

37. Henkel, N.D., Wu, X., O'Donovan, S.M. et al. Schizophrenia: a disorder of broken brain bioenergetics. Mol Psychiatry 27, 2393–2404 (2022). https://doi.org/10.1038/s41380-022-01494-x

38. Hartmann C, Kempf A. Mitochondrial control of sleep. Curr Opin Neurobiol. 2023 Aug;81:102733. doi: 10.1016/j.conb.2023.102733.

39. Richardson RB, Mailloux RJ. Mitochondria Need Their Sleep: Redox, Bioenergetics, and Temperature Regulation of Circadian Rhythms and the Role of Cysteine-Mediated Redox Signaling, Uncoupling Proteins, and Substrate Cycles. Antioxidants (Basel). 2023 Mar 9;12(3):674. doi: 10.3390/antiox12030674.

40. A. A. Denis, D. Toledo, Q. A. Hakim, A. A. Quintana, C. R. Escobar, S. A. Oluwole, A. Costa, E. G. Garcia, A. R. Hill, C. Agatemor, Ligand-Independent Activation of Aryl Hydrocarbon Receptor and Attenuation of Glutamine Levels by Natural Deep Eutectic Solvent. ChemBioChem 2023, 24, e202300540.

41. Hayakawa, K., Esposito, E., Wang, X. et al. Transfer of mitochondria from astrocytes to neurons after stroke. Nature 535, 551–555 (2016). https://doi.org/10.1038/nature18928

42. Gollihue JL, Norris CM. Astrocyte mitochondria: Central players and potential therapeutic targets for neurodegenerative diseases and injury. Ageing Res Rev. 2020 May;59:101039. doi: 10.1016/j.arr.2020.101039.

43. Misgeld T, Schwarz TL. Mitostasis in Neurons: Maintaining Mitochondria in an Extended Cellular Architecture. Neuron. 2017 Nov 1;96(3):651-666. doi: 10.1016/j.neuron.2017.09.055. PMID: 29096078; PMCID: PMC5687842.

44. Downar J., Crawley A. P., Mikulis D. J., Davis K. D. (2000). A multimodal cortical network for the detection of changes in the sensory environment. Nat. Neurosci. 3 277–283. 10.1038/72991

45. Wolff M., Vann S. D. (2019). The cognitive thalamus as a gateway to mental representations. J. Neurosci. 39 3–14. 10.1523/JNEUROSCI.0479-18.2018

46. Sridharan D, Levitin DJ, Menon V. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc Natl Acad Sci USA. 2008;105(34):12569–12574.

47. Ueno D, Matsuoka T, Kato Y, Ayani N, Maeda S, Takeda M, Narumoto J. Individual Differences in Interoceptive Accuracy Are Correlated With Salience Network Connectivity in Older Adults. Front Aging Neurosci. 2020 Dec 1;12:592002. doi: 10.3389/fnagi.2020.592002.

48. Blessing WW, Blessing EM, Mohammed M, Ootsuka Y. Clozapine, chlorpromazine and risperidone dose-dependently reduce emotional hyperthermia, a biological marker of salience. Psychopharmacology (Berl). 2017 Nov;234(21):3259-3269. doi: 10.1007/s00213-017-4710-x.

49. Seeley WW. The Salience Network: A Neural System for Perceiving and Responding to Homeostatic Demands. J Neurosci. 2019 Dec 11;39(50):9878-9882. doi: 10.1523/JNEUROSCI.1138-17.2019.

50. Pasquini L, Nana AL, Toller G, Brown JA, Deng J, Staffaroni A, Kim EJ, Hwang JL, Li L, Park Y, Gaus SE, Allen I, Sturm VE, Spina S, Grinberg LT, Rankin KP, Kramer JH, Rosen HJ, Miller BL, Seeley WW. Salience Network Atrophy Links Neuron Type-Specific Pathobiology to Loss of Empathy in Frontotemporal Dementia. Cereb Cortex. 2020 Sep 3;30(10):5387-5399. doi: 10.1093/cercor/bhaa119.

51. Mendez MF, Anderson E, Shapira JS. An investigation of moral judgement in frontotemporal dementia. Cogn Behav Neurol. 2005 Dec;18(4):193-7. doi: 10.1097/01.wnn.0000191292.17964.bb.

52. Mendez MF. The neurobiology of moral behavior: review and neuropsychiatric implications. CNS Spectr. 2009 Nov;14(11):608-20. doi: 10.1017/s1092852900023853.

53. Boeve BF. Behavioral Variant Frontotemporal Dementia. Continuum (Minneap Minn). 2022 Jun 1;28(3):702-725. doi: 10.1212/CON.0000000000001105.

54. Arrigoni E, Fuller PM. The Sleep-Promoting Ventrolateral Preoptic Nucleus: What Have We Learned over the Past 25 Years? Int J Mol Sci. 2022 Mar 8;23(6):2905. doi: 10.3390/ijms23062905.

55. De Luca, R., Nardone, S., Grace, K.P. et al. Orexin neurons inhibit sleep to promote arousal. Nat Commun 13, 4163 (2022). https://doi.org/10.1038/s41467-022-31591-y

56. Inutsuka A, Yamanaka A. The regulation of sleep and wakefulness by the hypothalamic neuropeptide orexin/hypocretin. Nagoya J Med Sci. 2013 Feb;75(1-2):29-36.

57. Yin D, Dong H, Wang TX, Hu ZZ, Cheng NN, Qu WM, Huang ZL. Glutamate Activates the Histaminergic Tuberomammillary Nucleus and Increases Wakefulness in Rats. Neuroscience. 2019 Aug 10;413:86-98. doi: 10.1016/j.neuroscience.2019.05.032.

58. Konadhode RR, Pelluru D, Shiromani PJ. Neurons containing orexin or melanin concentrating hormone reciprocally regulate wake and sleep. Front Syst Neurosci. 2015 Jan 8;8:244. doi: 10.3389/fnsys.2014.00244.

59. Chung S, Weber F, Zhong P, Tan CL, Nguyen TN, Beier KT, Hörmann N, Chang WC, Zhang Z, Do JP, Yao S, Krashes MJ, Tasic B, Cetin A, Zeng H, Knight ZA, Luo L, Dan Y. Identification of preoptic sleep neurons using retrograde labelling and gene profiling. Nature. 2017 May 25;545(7655):477-481. doi: 10.1038/nature22350.

60. Bandarabadi, M., Li, S., Aeschlimann, L. et al. Inactivation of hypocretin receptor-2 signaling in dopaminergic neurons induces hyperarousal and enhanced cognition but impaired inhibitory control. Mol Psychiatry (2023). https://doi.org/10.1038/s41380-023-02329-z

61. S. Wu, C. Gao, F. Han, H. Cheng, Histamine H1 receptor in basal forebrain cholinergic circuit: A novel target for the negative symptoms of schizophrenia? Neurosci. Bull. 38, 558–560 (2022).

62. Grady FS, Boes AD, Geerling JC. A Century Searching for the Neurons Necessary for Wakefulness. Front Neurosci. 2022 Jul 19;16:930514. doi: 10.3389/fnins.2022.930514.

63. Kerkhofs M, Lavie P. Frédéric Bremer 1892-1982: a pioneer in sleep research. Sleep Med Rev. 2000 Oct;4(5):505-14. doi: 10.1053/smrv.2000.0112. PMID: 17210279.

64. Fuller PM, Sherman D, Pedersen NP, Saper CB, Lu J. Reassessment of the structural basis of the ascending arousal system. J Comp Neurol. 2011 Apr 1;519(5):933-56. doi: 10.1002/cne.22559. Erratum in: J Comp Neurol. 2011 Dec 15;519(18):3817. Fuller, Patrick (corrected to Fuller, Patrick M).

65. Lavie P. The sleep theory of Constantin von Economo. J Sleep Res. 1993 Sep;2(3):175-178. doi: 10.1111/j.1365-2869.1993.tb00083.x. PMID: 10607091.

66. Vyas A, De Jesus O. Von Economo Encephalitis. 2023 Aug 23. In: StatPearls (Internet). Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 33620860.

67. Rosen D. Asleep: the Forgotten Epidemic That Remains One of Medicine's Greatest Mysteries. J Clin Sleep Med. 2010 Jun 15;6(3):299. PMCID: PMC2883045.

68. Cortelli P, Perani D, Parchi P, Grassi F, Montagna P, De Martin M, Castellani R, Tinuper P, Gambetti P, Lugaresi E, Fazio F. Cerebral metabolism in fatal familial insomnia: relation to duration, neuropathology, and distribution of protease-resistant prion protein. Neurology. 1997 Jul;49(1):126-33. doi: 10.1212/wnl.49.1.126.

69. Gallassi R, Morreale A, Montagna P, Cortelli P, Avoni P, Castellani R, Gambetti P, Lugaresi E. Fatal familial insomnia: behavioral and cognitive features. Neurology. 1996 Apr;46(4):935-9. doi: 10.1212/wnl.46.4.935.

70. Sturm VE, Brown JA, Hua AY, Lwi SJ, Zhou J, Kurth F, Eickhoff SB, Rosen HJ, Kramer JH, Miller BL, Levenson RW, Seeley WW. Network Architecture Underlying Basal Autonomic Outflow: Evidence from Frontotemporal Dementia. J Neurosci. 2018 Oct 17;38(42):8943-8955. doi: 10.1523/JNEUROSCI.0347-18.2018.

71. Mallikarjun, P.K., Lalousis, P.A., Dunne, T.F. et al. Aberrant salience network functional connectivity in auditory verbal hallucinations: a first episode psychosis sample. Transl Psychiatry 8, 69 (2018). https://doi.org/10.1038/s41398-018-0118-6

72. Cracco L, Appleby BS, Gambetti P. Fatal familial insomnia and sporadic fatal insomnia. Handb Clin Neurol. 2018;153:271-299. doi: 10.1016/B978-0-444-63945-5.00015-5.

73. Wang Y, Li M, Li W, Xiao L, Huo X, Ding J, Sun T. Is the insula linked to sleep? A systematic review and narrative synthesis. Heliyon. 2022 Nov 5;8(11):e11406. doi: 10.1016/j.heliyon.2022.e11406.

74. Levichkina EV, Busygina II, Pigareva ML, Pigarev IN. The Mysterious Island: Insula and Its Dual Function in Sleep and Wakefulness. Front Syst Neurosci. 2021 Feb 11;14:592660. doi: 10.3389/fnsys.2020.592660.

75. Guo Y, Zou G, Shao Y, Chen J, Li Y, Liu J, Yao P, Zhou S, Xu J, Hu S, Gao JH, Zou Q, Sun H. Increased connectivity of the anterior cingulate cortex is associated with the tendency to awakening during N2 sleep in patients with insomnia disorder. Sleep. 2023 Mar 9;46(3):zsac290. doi: 10.1093/sleep/zsac290.

76. Guldenmund P, Demertzi A, Boveroux P, Boly M, Vanhaudenhuyse A, Bruno MA, Gosseries O, Noirhomme Q, Brichant JF, Bonhomme V, Laureys S, Soddu A. Thalamus, brainstem and salience network connectivity changes during propofol-induced sedation and unconsciousness. Brain Connect. 2013;3(3):273-85. doi: 10.1089/brain.2012.0117.

77. Zhang L, Luo L, Zhou Z, Xu K, Zhang L, Liu X, Tan X, Zhang J, Ye X, Gao J, Luo B. Functional Connectivity of Anterior Insula Predicts Recovery of Patients With Disorders of Consciousness. Front Neurol. 2018 Nov 30;9:1024. doi: 10.3389/fneur.2018.01024.

78. Mashour GA. Anesthetizing the Self: The Neurobiology of Humbug. Anesthesiology. 2016 Apr;124(4):747-9. doi: 10.1097/ALN.0000000000001028. PMID: 26808635.

79. Qi J, Li BZ, Zhang Y, Pan B, Gao YH, Zhan H, Liu Y, Shao YC, Zhang X. Altered insula-prefrontal functional connectivity correlates to decreased vigilant attention after total sleep deprivation. Sleep Med. 2021 Aug;84:187-194. doi: 10.1016/j.sleep.2021.05.037.

80. Li C, Dong M, Yin Y, Hua K, Fu S, Jiang G. Aberrant Effective Connectivity of the Right Anterior Insula in Primary Insomnia. Front Neurol. 2018 May 8;9:317. doi: 10.3389/fneur.2018.00317.

81. Chen MC, Chiang WY, Yugay T, Patxot M, Özçivit İB, Hu K, Lu J. Anterior Insula Regulates Multiscale Temporal Organization of Sleep and Wake Activity. J Biol Rhythms. 2016 Apr;31(2):182-93. doi: 10.1177/0748730415627035.

82. Palaniyappan L, White TP, Liddle PF. The concept of salience network dysfunction in schizophrenia: from neuroimaging observations to therapeutic opportunities. Curr Top Med Chem. 2012;12(21):2324-38. doi: 10.2174/156802612805289881.

83. Huang, H., Chen, C., Rong, B. et al. Resting-state functional connectivity of salience network in schizophrenia and depression. Sci Rep 12, 11204 (2022). https://doi.org/10.1038/s41598-022-15489-9

84. He X, Qin W, Liu Y, Zhang X, Duan Y, Song J, Li K, Jiang T, Yu C. Abnormal salience network in normal aging and in amnestic mild cognitive impairment and Alzheimer's disease. Hum Brain Mapp. 2014 Jul;35(7):3446-64. doi: 10.1002/hbm.22414.

85. Putcha D, Ross RS, Cronin-Golomb A, Janes AC, Stern CE. Salience and Default Mode Network Coupling Predicts Cognition in Aging and Parkinson's Disease. J Int Neuropsychol Soc. 2016 Feb;22(2):205-15. doi: 10.1017/S1355617715000892.

86. Day GS, Farb NAS, Tang-Wai DF, et al. Salience Network Resting-State Activity: Prediction of Frontotemporal Dementia Progression. JAMA Neurol. 2013;70(10):1249–1253. doi:10.1001/jamaneurol.2013.3258

87. Sheffield JM, Rogers BP, Blackford JU, Heckers S, Woodward ND. Insula functional connectivity in schizophrenia. Schizophr Res. 2020 Jun;220:69-77. doi: 10.1016/j.schres.2020.03.068.

88. Adams R, David AS. Patterns of anterior cingulate activation in schizophrenia: a selective review. Neuropsychiatr Dis Treat. 2007 Feb;3(1):87-101. doi: 10.2147/nedt.2007.3.1.87.

89. Finger EC. Frontotemporal Dementias. Continuum (Minneap Minn). 2016 Apr;22(2 Dementia):464-89. doi: 10.1212/CON.0000000000000300. PMID: 27042904; PMCID: PMC5390934.

90. Zago S, Scarpazza C, Difonzo T, Arighi A, Hajhajate D, Torrente Y, Sartori G. Behavioral Variant of Frontotemporal Dementia and Homicide in a Historical Case. J Am Acad Psychiatry Law. 2021 Jun;49(2):219-227. doi: 10.29158/JAAPL.200081-20.

91. Nilsson C, Landqvist Waldö M, Nilsson K, et al. Age-related incidence and family history in frontotemporal dementia: data from the Swedish Dementia Registry. PLoS One 2014;9(4). doi: 10.1371/journal.pone.0094901

92. Hendriks S, Peetoom K, Bakker C, van der Flier WM, Papma JM, Koopmans R, Verhey FRJ, de Vugt M, Köhler S. Global Prevalence of Young-Onset Dementia: A Systematic Review and Meta-analysis. JAMA Neurol. 2021 Sep 1;78(9):1080-1090. doi: 10.1001/jamaneurol.2021.2161.

93. Onyike CU, Diehl-Schmid J. The epidemiology of frontotemporal dementia. Int Rev Psychiatry. 2013 Apr;25(2):130-7. doi: 10.3109/09540261.2013.776523. PMID: 23611343

94. Diehl-Schmid J, Perneczky R, Koch J, Nedopil N, Kurz A. Guilty by suspicion? Criminal behavior in frontotemporal lobar degeneration. Cogn Behav Neurol (2013) 26(2):73–7 10.1097/WNN.0b013e31829cff11

95. Krause M, Theiss C, Brüne M. Ultrastructural Alterations of Von Economo Neurons in the Anterior Cingulate Cortex in Schizophrenia. Anat Rec (Hoboken). 2017 Nov;300(11):2017-2024. doi: 10.1002/ar.23635.

96. Nana AL, Sidhu M, Gaus SE, Hwang JL, Li L, Park Y, Kim EJ, Pasquini L, Allen IE, Rankin KP, Toller G, Kramer JH, Geschwind DH, Coppola G, Huang EJ, Grinberg LT, Miller BL, Seeley WW. Neurons selectively targeted in frontotemporal dementia reveal early stage TDP-43 pathobiology. Acta Neuropathol. 2019 Jan;137(1):27-46. doi: 10.1007/s00401-018-1942-8.

97. Vohryzek J, Cabral J, Vuust P, Deco G, Kringelbach ML. Understanding brain states across spacetime informed by whole-brain modelling. Philos Trans A Math Phys Eng Sci. 2022 Jul 11;380(2227):20210247. doi: 10.1098/rsta.2021.0247

98. Nathani M, Jaleel V, Turner A, et al: When you hear hoofbeats, think horses and zebras: the importance of a wide differential when it comes to frontotemporal lobar degeneration. Asian J Psychiatr 47:101875, 2020

99. Herbert BM, Herbert C, Pollatos O. On the relationship between interoceptive awareness and alexithymia: is interoceptive awareness related to emotional awareness? J Pers. 2011 Oct;79(5):1149-75. doi: 10.1111/j.1467-6494.2011.00717.x.

100. Quadt L, Critchley HD, Garfinkel SN. The neurobiology of interoception in health and disease. Ann N Y Acad Sci. 2018 Sep;1428(1):112-128. doi: 10.1111/nyas.13915.

101. Cauda F, Geminiani GC, Vercelli A. Evolutionary appearance of von Economo's neurons in the mammalian cerebral cortex. Front Hum Neurosci. 2014 Mar 14;8:104. doi: 10.3389/fnhum.2014.00104.

102. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct. 2010 Jun;214(5-6):655-67. doi: 10.1007/s00429-010-0262-0.

103. López-Ojeda W, Hurley RA. Von Economo Neuron Involvement in Social Cognitive and Emotional Impairments in Neuropsychiatric Disorders. J Neuropsychiatry Clin Neurosci. 2022 Fall;34(4):302-306. doi: 10.1176/appi.neuropsych.20220136.

104. Hodge, R.D., Miller, J.A., Novotny, M. et al. Transcriptomic evidence that von Economo neurons are regionally specialized extratelencephalic-projecting excitatory neurons. Nat Commun 11, 1172 (2020). https://doi.org/10.1038/s41467-020-14952-3

105. Anke A Dijkstra, Li-Chun Lin, Alissa L Nana, Stephanie E Gaus, William W Seeley, Von Economo Neurons and Fork Cells: A Neurochemical Signature Linked to Monoaminergic Function, Cerebral Cortex, Volume 28, Issue 1, January 2018, Pages 131–144, https://doi.org/10.1093/cercor/bhw358

106. Azizi SA. Monoamines: Dopamine, Norepinephrine, and Serotonin, Beyond Modulation, "Switches" That Alter the State of Target Networks. Neuroscientist. 2022 Apr;28(2):121-143. doi: 10.1177/1073858420974336

107. Valli M, Cho SS, Uribe C, Masellis M, Chen R, Mihaescu A, Strafella AP. VMAT2 availability in Parkinson's disease with probable REM sleep behaviour disorder. Mol Brain. 2021 Nov 10;14(1):165. doi: 10.1186/s13041-021-00875-7.

108. Broese M, Riemann D, Hein L, Nissen C. α-Adrenergic receptor function, arousal and sleep: mechanisms and therapeutic implications. Pharmacopsychiatry. 2012 Sep;45(6):209-16. doi: 10.1055/s-0031-1299728.

109. Clark DA, Mancama D, Kerwin RW, Arranz MJ. Expression of the alpha1A-adrenergic receptor in schizophrenia. Neurosci Lett. 2006 Jul 3;401(3):248-51. doi: 10.1016/j.neulet.2006.03.025.

110. Sjögren M, Minthon L, Passant U, Blennow K, Wallin A. Decreased monoamine metabolites in frontotemporal dementia and Alzheimer's disease. Neurobiol Aging. 1998 Sep-Oct;19(5):379-84. doi: 10.1016/s0197-4580(98)00086-4. PMID: 9880039.

111. Levenson JC, Kay DB, Buysse DJ. The pathophysiology of insomnia. Chest. 2015 Apr;147(4):1179-1192. doi: 10.1378/chest.14-1617. PMID: 25846534; PMCID: PMC4388122

112. Kiyoshi CM, Zhou M. Astrocyte syncytium: a functional reticular system in the brain. Neural Regen Res. 2019 Apr;14(4):595-596. doi: 10.4103/1673-5374.247462.

113. Garofalo, S., Picard, K., Limatola, C., Nadjar, A., Pascual, O., and Tremblay, M. E. (2020). Role of Glia in the Regulation of Sleep in Health and Disease. Compr Physiol 10, 101.245. doi: 10.1002/cphy.c190022

114. Que M, Li Y, Wang X, Zhan G, Luo X, Zhou Z. Role of astrocytes in sleep deprivation: accomplices, resisters, or bystanders? Front Cell Neurosci. 2023 Jun 26;17:1188306. doi: 10.3389/fncel.2023.118830

115. Mader S, Brimberg L. Aquaporin-4 Water Channel in the Brain and Its Implication for Health and Disease. Cells. 2019 Jan 27;8(2):90. doi: 10.3390/cells8020090.

116. Jessen NA, Munk AS, Lundgaard I, Nedergaard M. The Glymphatic System: A Beginner's Guide. Neurochem Res. 2015 Dec;40(12):2583-99. doi: 10.1007/s11064-015-1581-6.

117. Valenti D, Vacca RA, Moro L, Atlante A. Mitochondria Can Cross Cell Boundaries: An Overview of the Biological Relevance, Pathophysiological Implications and Therapeutic Perspectives of Intercellular Mitochondrial Transfer. Int J Mol Sci. 2021 Aug 2;22(15):8312. doi: 10.3390/ijms22158312.

118. Leow, D.M.-K.; Cheah, I.K.-M.; Fong, Z.W.-J.; Halliwell, B.; Ong, W.-Y. Protective Effect of Ergothioneine against 7-Ketocholesterol-Induced Mitochondrial Damage in hCMEC/D3 Human Brain Endothelial Cells. Int. J. Mol. Sci. 2023, 24, 5498. https://doi.org/10.3390/ijms24065498

119. Nicolson GL. Mitochondrial Dysfunction and Chronic Disease: Treatment With Natural Supplements. Integr Med (Encinitas). 2014 Aug;13(4):35-43.

120. Hill VM, O'Connor RM, Sissoko GB, Irobunda IS, Leong S, Canman JC, Stavropoulos N, Shirasu-Hiza M. A bidirectional relationship between sleep and oxidative stress in Drosophila. PLoS Biol. 2018 Jul 12;16(7):e2005206. doi: 10.1371/journal.pbio.2005206.

121. Patergnani S, Bonora M, Ingusci S, Previati M, Marchi S, Zucchini S, Perrone M, Wieckowski MR, Castellazzi M, Pugliatti M, Giorgi C, Simonato M, Pinton P. Antipsychotic drugs counteract autophagy and mitophagy in multiple sclerosis. Proc Natl Acad Sci U S A. 2021 Jun 15;118(24):e2020078118. doi: 10.1073/pnas.2020078118.

122. Hirata Y, Cai R, Volchuk A, et al. Lipid peroxidation increases membrane tension, Piezo1 gating, and cation permeability to execute ferroptosis. Current Biology : CB. 2023 Apr;33(7):1282-1294.e5. DOI: 10.1016/j.cub.2023.02.060. PMID: 36898371.

123. Heckers S, Konradi C. Hippocampal neurons in schizophrenia. J Neural Transm (Vienna). 2002 May;109(5-6):891-905. doi: 10.1007/s007020200073.

124. Padurariu M, Ciobica A, Mavroudis I, Fotiou D, Baloyannis S. Hippocampal neuronal loss in the CA1 and CA3 areas of Alzheimer's disease patients. Psychiatr Danub. 2012 Jun;24(2):152-8. PMID: 22706413.

125. Zhang P, Li YX, Zhang ZZ, Yang Y, Rao JX, Xia L, Li XY, Chen GH, Wang F. Astroglial Mechanisms Underlying Chronic Insomnia Disorder: A Clinical Study. Nat Sci Sleep. 2020 Oct 8;12:693-704. doi: 10.2147/NSS.S263528.

126. Bellesi M, de Vivo L, Chini M, Gilli F, Tononi G, Cirelli C. Sleep Loss Promotes Astrocytic Phagocytosis and Microglial Activation in Mouse Cerebral Cortex. J Neurosci. 2017 May 24;37(21):5263-5273. doi: 10.1523/JNEUROSCI.3981-16.2017.

127. Vilalta A, Brown GC. Neurophagy, the phagocytosis of live neurons and synapses by glia, contributes to brain development and disease. FEBS J. 2018 Oct;285(19):3566-3575. doi: 10.1111/febs.14323.

128. Liddelow, S., Guttenplan, K., Clarke, L. et al. Neurotoxic reactive astrocytes are induced by activated microglia. Nature 541, 481–487 (2017). https://doi.org/10.1038/nature21029

129. Whitehurst T, Howes O. The role of mitochondria in the pathophysiology of schizophrenia: A critical review of the evidence focusing on mitochondrial complex one. Neurosci Biobehav Rev. 2022 Jan;132:449-464. doi: 10.1016/j.neubiorev.2021.11.047

130. Melhuish Beaupre LM, Brown GM, Braganza NA, Kennedy JL, Gonçalves VF. Mitochondria's role in sleep: Novel insights from sleep deprivation and restriction studies. World J Biol Psychiatry. 2022 Jan;23(1):1-13. doi: 10.1080/15622975.2021.1907723.

131. Richardson RB, Mailloux RJ. Mitochondria Need Their Sleep: Redox, Bioenergetics, and Temperature Regulation of Circadian Rhythms and the Role of Cysteine-Mediated Redox Signaling, Uncoupling Proteins, and Substrate Cycles. Antioxidants (Basel). 2023 Mar 9;12(3):674. doi: 10.3390/antiox12030674.

132. Ene H.M., Karry R., Farfara D., Ben-Shachar D. Mitochondria play an essential role in the trajectory of adolescent neurodevelopment and behavior in adulthood: Evidence from a schizophrenia rat model. Mol. Psychiatry. 2023;28:1170–1181. doi: 10.1038/s41380-022-01865-4.

133. Wang X, Wang W, Li L, Perry G, Lee HG, Zhu X. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. Biochim Biophys Acta. 2014 Aug;1842(8):1240-7. doi: 10.1016/j.bbadis.2013.10.015.

134. Heo MJ, Suh JH, Lee SH, Poulsen KL, An YA, Moorthy B, Hartig SM, Moore DD, Kim KH. Aryl hydrocarbon receptor maintains hepatic mitochondrial homeostasis in mice. Mol Metab. 2023 Jun;72:101717. doi: 10.1016/j.molmet.2023.101717.

135. Hwang HJ, Dornbos P, Steidemann M, Dunivin TK, Rizzo M, LaPres JJ. Mitochondrial-targeted aryl hydrocarbon receptor and the impact of 2,3,7,8-tetrachlorodibenzo-p-dioxin on cellular respiration and the mitochondrial proteome. Toxicol Appl Pharmacol. 2016 Aug 1;304:121-32. doi: 10.1016/j.taap.2016.04.005.

136. Heath-Pagliuso S, Rogers WJ, Tullis K, Seidel SD, Cenijn PH, Brouwer A, Denison MS. Activation of the Ah receptor by tryptophan and tryptophan metabolites. Biochemistry. 1998 Aug 18;37(33):11508-15. doi: 10.1021/bi980087p.

137. Slominski AT, Kim TK, Slominski RM, Song Y, Qayyum S, Placha W, Janjetovic Z, Kleszczyński K, Atigadda V, Song Y, Raman C, Elferink CJ, Hobrath JV, Jetten AM, Reiter RJ. Melatonin and Its Metabolites Can Serve as Agonists on the Aryl Hydrocarbon Receptor and Peroxisome Proliferator-Activated Receptor Gamma. Int J Mol Sci. 2023 Oct 23;24(20):15496. doi: 10.3390/ijms242015496.

138. Xu CX, Wang C, Krager SL, Bottum KM, Tischkau SA. Aryl hydrocarbon receptor activation attenuates Per1 gene induction and influences circadian clock resetting. Toxicol Sci. 2013 Apr;132(2):368-78. doi: 10.1093/toxsci/kfs345.

139. Hartmann C, Kempf A. Mitochondrial control of sleep. Curr Opin Neurobiol. 2023 Aug;81:102733. doi: 10.1016/j.conb.2023.102733

140. Wei, Y., Helleberg, H., Rannug, U. & Rannug, A. Rapid and transient induction of CYP1A1 gene expression in human cells by the tryptophan photoproduct 6-formylindolo(3,2-b)carbazole. Chem. Biol. Interact. 110, 39–55 (1998).

141. Ziv-Gal A, Flaws JA, Mahoney MM, Miller SR, Zacur HA, Gallicchio L. Genetic polymorphisms in the aryl hydrocarbon receptor-signaling pathway and sleep disturbances in middle-aged women. Sleep Med. 2013 Sep;14(9):883-7. doi: 10.1016/j.sleep.2013.04.007.

142. Frau-Méndez MA, Fernández-Vega I, Ansoleaga B, Blanco Tech R, Carmona Tech M, Antonio Del Rio J, Zerr I, Llorens F, José Zarranz J, Ferrer I. Fatal familial insomnia: mitochondrial and protein synthesis machinery decline in the mediodorsal thalamus. Brain Pathol. 2017 Jan;27(1):95-106. doi: 10.1111/bpa.12408.

143. Kishikawa JI, Inoue Y, Fujikawa M, Nishimura K, Nakanishi A, Tanabe T, Imamura H, Yokoyama K. General anesthetics cause mitochondrial dysfunction and reduction of intracellular ATP levels. PLoS One. 2018 Jan 3;13(1):e0190213. doi: 10.1371/journal.pone.0190213.

144. Wei H. The role of calcium dysregulation in anesthetic-mediated neurotoxicity. Anesth Analg. 2011 Nov;113(5):972-4. doi: 10.1213/ANE.0b013e3182323261.

145. Lee, H. G., Choi, S. I., Park, S. K., Park, S. J., Kim, N. H., and Choi, E. K. (2000). Alteration of glutathione metabolism and abnormal calcium accumulation in the mitochondria of hamster brain infected with scrapie agent. Neurobiol. Aging 21:151. doi: 10.1016/s0197-4580(00)82014-x

146. Glatzel M, Sepulveda-Falla D. Losing sleep over mitochondria: a new player in the pathophysiology of fatal familial insomnia. Brain Pathol. 2017 Jan;27(1):107-108. doi: 10.1111/bpa.12410. PMID: 27350067; PMCID: PMC8028983.

147. Moon JH, Park SY. Prion peptide-mediated calcium level alteration governs neuronal cell damage through AMPK-autophagy flux. Cell Commun Signal. 2020 Jul 11;18(1):109. doi: 10.1186/s12964-020-00590-1

148. Matteoni S, Matarrese P, Ascione B, Ricci-Vitiani L, Pallini R, Villani V, Pace A, Paggi MG, Abbruzzese C. Chlorpromazine induces cytotoxic autophagy in glioblastoma cells via endoplasmic reticulum stress and unfolded protein response. J Exp Clin Cancer Res. 2021 Nov 5;40(1):347. doi: 10.1186/s13046-021-02144-w

149. Barreca ML, Iraci N, Biggi S, Cecchetti V, Biasini E. Pharmacological Agents Targeting the Cellular Prion Protein. Pathogens. 2018 Mar 7;7(1):27. doi: 10.3390/pathogens7010027. PMID: 29518975; PMCID: PMC5874753.

150. Korth C, May BC, Cohen FE, Prusiner SB. Acridine and phenothiazine derivatives as pharmacotherapeutics for prion disease. Proc Natl Acad Sci U S A. 2001 Aug 14;98(17):9836-41. doi: 10.1073/pnas.161274798.

151. Khattar KE, Safi J, Rodriguez AM, Vignais ML. Intercellular Communication in the Brain through Tunneling Nanotubes. Cancers (Basel). 2022 Feb 25;14(5):1207. doi: 10.3390/cancers14051207.

152. Wang, X., Gerdes, HH. Transfer of mitochondria via tunneling nanotubes rescues apoptotic PC12 cells. Cell Death Differ 22, 1181–1191 (2015). https://doi.org/10.1038/cdd.2014.211

153. Savaskan NE, Borchert A, Bräuer AU, Kuhn H. Role for glutathione peroxidase-4 in brain development and neuronal apoptosis: specific induction of enzyme expression in reactive astrocytes following brain injury. Free Radic Biol Med. 2007 Jul 15;43(2):191-201. doi: 10.1016/j.freeradbiomed.2007.03.033.

154. Mauri S, Favaro M, Bernardo G, Mazzotta GM, Ziviani E. Mitochondrial autophagy in the sleeping brain. Front Cell Dev Biol. 2022 Aug 24;10:956394. doi: 10.3389/fcell.2022.956394.

155. Chen S, Owens GC, Crossin KL, Edelman DB. Serotonin stimulates mitochondrial transport in hippocampal neurons. Mol Cell Neurosci. 2007 Dec;36(4):472-83. doi: 10.1016/j.mcn.2007.08.004.

156. Lin LC, Nana AL, Hepker M, Hwang JL, Gaus SE, Spina S, Cosme CG, Gan L, Grinberg LT, Geschwind DH, Coppola G, Rosen HJ, Miller BL, Seeley WW. Preferential tau aggregation in von Economo neurons and fork cells in frontotemporal lobar degeneration with specific MAPT variants. Acta Neuropathol Commun. 2019 Oct 22;7(1):159. doi: 10.1186/s40478-019-0809-0. P

157. Hogan DB, Jetté N, Fiest KM, Roberts JI, Pearson D, Smith EE, Roach P, Kirk A, Pringsheim T, Maxwell CJ. The Prevalence and Incidence of Frontotemporal Dementia: a Systematic Review. Can J Neurol Sci. 2016 Apr;43 Suppl 1:S96-S109. doi: 10.1017/cjn.2016.25.

158. Course MM, Wang X. Transporting mitochondria in neurons. F1000Res. 2016 Jul 18;5:F1000 Faculty Rev-1735. doi: 10.12688/f1000research.7864.1. PMID: 27508065; PMCID: PMC4955021.

159. Nuñez MT, Chana-Cuevas P. New Perspectives in Iron Chelation Therapy for the Treatment of Neurodegenerative Diseases. Pharmaceuticals (Basel). 2018 Oct 19;11(4):109. doi: 10.3390/ph11040109

160. Kupershmidt, L.; Youdim, M.B.H. The Neuroprotective Activities of the Novel Multi-Target Iron-Chelators in Models of Alzheimer's Disease, Amyotrophic Lateral Sclerosis and Aging. Cells 2023, 12, 763. https://doi.org/10.3390/cells12050763

161. Calderón-Montaño JM, Burgos-Morón E, Pérez-Guerrero C, López-Lázaro M. A review on the dietary flavonoid kaempferol. Mini Rev Med Chem. 2011 Apr;11(4):298-344. doi: 10.2174/138955711795305335. PMID: 21428901.

162. Du YY, Sun T, Yang Q, Liu QQ, Li JM, Yang L, Luo LX. Therapeutic Potential of Kaempferol against Sleep Deprivation-Induced Cognitive Impairment: Modulation of Neuroinflammation and Synaptic Plasticity Disruption in Mice. ACS Pharmacol Transl Sci. 2023 Nov 30;6(12):1934-1944. doi: 10.1021/acsptsci.3c00226.

163. Saleem A, Qurat-Ul-Ain, Akhtar MF. Alternative Therapy of Psychosis: Potential Phytochemicals and Drug Targets in the Management of Schizophrenia. Front Pharmacol. 2022 May 17;13:895668. doi: 10.3389/fphar.2022.895668.

164. Zhou M, Ren H, Han J, Wang W, Zheng Q, Wang D. Protective Effects of Kaempferol against Myocardial Ischemia/Reperfusion Injury in Isolated Rat Heart via Antioxidant Activity and Inhibition of Glycogen Synthase Kinase-3β. Oxid Med Cell Longev. 2015;2015:481405. doi: 10.1155/2015/481405.

165. Jope RS, Roh MS. Glycogen synthase kinase-3 (GSK3) in psychiatric diseases and therapeutic interventions. Curr Drug Targets. 2006 Nov;7(11):1421-34. doi: 10.2174/1389450110607011421.

166. Mohammad MK, Al-Masri IM, Taha MO, Al-Ghussein MA, Alkhatib HS, Najjar S, Bustanji Y. Olanzapine inhibits glycogen synthase kinase-3beta: an investigation by docking simulation and experimental validation. Eur J Pharmacol. 2008 Apr 14;584(1):185-91. doi: 10.1016/j.ejphar.2008.01.019.

167. Shilovsky, G.A., Putyatina, T.S., Morgunova, G.V. et al. A Crosstalk between the Biorhythms and Gatekeepers of Longevity: Dual Role of Glycogen Synthase Kinase-3. Biochemistry Moscow 86, 433–448 (2021). https://doi.org/10.1134/S0006297921040052

168. Dozza B, Smith MA, Perry G, Tabaton M, Strocchi P. Regulation of glycogen synthase kinase-3beta by products of lipid peroxidation in human neuroblastoma cells. J Neurochem. 2004 Jun;89(5):1224-32. doi: 10.1111/j.1471-4159.2004.02413.x.

169. Agmon, E., Solon, J., Bassereau, P. et al. Modeling the effects of lipid peroxidation during ferroptosis on membrane properties. Sci Rep 8, 5155 (2018). https://doi.org/10.1038/s41598-018-23408-0

170. Serafim, B.; Bernardino, A.R.; Freitas, F.; Torres, C.A.V. Recent Developments in the Biological Activities, Bioproduction, and Applications of Pseudomonas spp. Phenazines. Molecules 2023, 28, 1368. https://doi.org/10.3390/molecules28031368

171. Jiang J, Guiza Beltran D, Schacht A, Wright S, Zhang L, Du L. Functional and Structural Analysis of Phenazine O-Methyltransferase LaPhzM from Lysobacter antibioticus OH13 and One-Pot Enzymatic Synthesis of the Antibiotic Myxin. ACS Chem Biol. 2018 Apr 20;13(4):1003-1012. doi: 10.1021/acschembio.8b00062.

172. Ohlendorf B, Schulz D, Erhard A, Nagel K, Imhoff JF. Geranylphenazinediol, an acetylcholinesterase inhibitor produced by a Streptomyces species. J Nat Prod. 2012 Jul 27;75(7):1400-4. doi: 10.1021/np2009626.

173. Rusman Y., Oppegard L.M., Hiasa H., Gelbmann C., Salomon C.E. Solphenazines A−F, glycosylated phenazines from Streptomyces sp. Strain DL-93. J. Nat. Prod. 2013;76:91–96. doi: 10.1021/np3007606.

174. Wang X., Abbas M., Zhang Y., Elshahawi S.I., Ponomareva L.V., Cui Z., Van Lanen S.G., Sajid I., Voss S.R., Shaaban K.A., et al. Baraphenazines A−G, divergent fused phenazine-based metabolites from a himalayan Streptomyces. J. Nat. Prod. 2019;82:1686–1693. doi: 10.1021/acs.jnatprod.9b00289

175. van Wezel, G. P.; McKenzie, N. L.; Nodwell, J. R. Chapter 5 Applying the genetics of secondary metabolism in model actinomycetes to the discovery of new antibiotics.; 1st ed.; Elsevier Inc., 2009; Vol. 458

176. Cha JW, Lee S, Kim MC, Thida M, Lee JW, Park JS, et al. Pontemazines a and B, phenazine derivatives containing a methylamine linkage from Streptomyces sp. UT1123 and their protective effect to HT-22 neuronal cells. Bioorganic & Medicinal Chemistry Letters. 2015;25:5083-5086. DOI: 10.1016/j.bmcl.2015.10.019

177. Krishnaiah M., Almeida N.R., Udumula V., Song Z., Chhonker Y.S., Abdelmoaty M.M., Nascimento V.A., Murry D.J., Conda-Sheridan M. Synthesis, biological evaluation, and metabolic stability of phenazine derivatives as antibacterial agents. Eur. J. Med. Chem. 2018;143:936–947. doi: 10.1016/j.ejmech.2017.11.026. (PubMed) (CrossRef) (Google Scholar)

178. Lavaggi M.L., Aguirre G.A., Boiani L., Orelli L., García B., Cerecetto H., González M. Pyrimido(1,2-a) quinoxaline 6-oxide and phenazine 5,10-dioxide derivatives and related compounds as growth inhibitors of Trypanosoma cruzi. Eur. J. Med. Chem. 2008;43:1737–1741. doi: 10.1016/j.ejmech.2007.10.031.

179. Kato S, Shindo K., Yamagishi Y., Matsuoka M., Kawai H., Mochizuki J. Phenazoviridin, a novel free radical scavenger from Streptomyces sp. taxonomy, fermentation, isolation, structure elucidation and biological properties. J. Antibiot. 1993;46:1485–1493. doi: 10.7164/antibiotics.46.1485.

180. Laxmi M., Bhat S.G. Characterization of pyocyanin with radical scavenging and antibiofilm properties isolated from Pseudomonas aeruginosa strain BTRY1. 3 Biotech. 2016;6:1–5. doi: 10.1007/s13205-015-0350-1

181. Nadeem A., Meijler MM. Unraveling the Antibacterial and Iron Chelating Activity of N-Oxide Hydroxy-Phenazine natural Products and Synthetic Analogs against Staphylococcus aureus. Israel Journal of Chemistry (2023) Volume63, Issue 5-6. https://doi.org/10.1002/ijch.202200112

182. Edinoff AN, Armistead G, Rosa CA, Anderson A, Patil R, Cornett EM, Murnane KS, Kaye AM, Kaye AD. Phenothiazines and their Evolving Roles in Clinical Practice: A Narrative Review. Health Psychol Res. 2022 Nov 3;10(4):38930. doi: 10.52965/001c.38930.

183. Heitmann ASB, Zanjani AAH, Klenow MB, Mularski A, Sønder SL, Lund FW, Boye TL, Dias C, Bendix PM, Simonsen AC, Khandelia H, Nylandsted J. Phenothiazines alter plasma membrane properties and sensitize cancer cells to injury by inhibiting annexin-mediated repair. J Biol Chem. 2021 Aug;297(2):101012. doi: 10.1016/j.jbc.2021.101012.

184. Boonnoy, P., Jarerattanachat, V., Karttunen, M. & Wong-ekkabut, J. Bilayer Deformation, Pores, and Micellation Induced by Oxidized Lipids. J. Phys. Chem. Lett. 6, 4884–4888 (2015).

185. Wu, CH., Bai, LY., Tsai, MH. et al. Pharmacological exploitation of the phenothiazine antipsychotics to develop novel antitumor agents–A drug repurposing strategy. Sci Rep 6, 27540 (2016). https://doi.org/10.1038/srep27540

186. Voronova O, Zhuravkov S, Korotkova E, Artamonov A, Plotnikov E. Antioxidant Properties of New Phenothiazine Derivatives. Antioxidants (Basel). 2022 Jul 14;11(7):1371. doi: 10.3390/antiox11071371

187. Keynes RG, Karchevskaya A, Riddall D, Griffiths CH, Bellamy TC, Chan AWE, Selwood DL, Garthwaite J. N10 -carbonyl-substituted phenothiazines inhibiting lipid peroxidation and associated nitric oxide consumption powerfully protect brain tissue against oxidative stress. Chem Biol Drug Des. 2019 Sep;94(3):1680-1693. doi: 10.1111/cbdd.13572.

188. Iuga C., Campero A., Vivier-Bunge A. Antioxidant vs. prooxidant action of phenothiazine in a biological environment in the presence of hydroxyl and hydroperoxyl radicals: A quantum chemistry study. RSC Adv. 2015;5:14678–14689. doi: 10.1039/C4RA14918A

189. Yue Y, Kong L, Wang J, Li C, Tan L, Su H, Xu Y. Regional Abnormality of Grey Matter in Schizophrenia: Effect from the Illness or Treatment? PLoS One. 2016 Jan 20;11(1):e0147204. doi: 10.1371/journal.pone.0147204.

190. Martínez A, Ibarra IA, Vargas R. A quantum chemical approach representing a new perspective concerning agonist and antagonist drugs in the context of schizophrenia and Parkinson's disease. PLoS One. 2019 Dec 12;14(12):e0224691. doi: 10.1371/journal.pone.0224691.

191. Goode-Romero G, Dominguez L, Martínez A. Electron Donor-Acceptor Properties of Different Muscarinic Ligands: On the Road to Control Schizophrenia. J Chem Inf Model. 2021 Oct 25;61(10):5117-5124. doi: 10.1021/acs.jcim.1c00780

192. Ho BC, Andreasen NC, Ziebell S, et al. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. Arch Gen Psychiatry 2011; 68: 128–137.

193. Veijola J, Guo JY, Moilanen JS, et al. Longitudinal changes in total brain volume in schizophrenia: relation to symptom severity, cognition antipsychotic medicatiom. PLoS One 2014; 9: 101689.

194. Engwa G.A., Ayuk E.L., Igbojekwe B.U., Unaegbu M. Potential Antioxidant Activity of New Tetracyclic and Pentacyclic Nonlinear Phenothiazine Derivatives. Biochem. Res. Int. 2016;2016:9896575. doi: 10.1155/2016/9896575.

195. Clark MA, Shay JW. Mitochondrial transformation of mammalian cells. Nature. (1982) 295:605–7. doi: 10.1038/295605a0

196. Katrangi E, D'Souza G, Boddapati SV, Kulawiec M, Singh KK, Bigger B, et al. Xenogenic transfer of isolated murine mitochondria into human rho0 cells can improve respiratory function. Rejuvenation Res. (2007) 10:561–70. doi: 10.1089/rej.2007.0575

197. Pacak AP, Preble JM, Kondo H, Seibel P, Levitsky S, del Nido PJ, et al. Actin-dependent mitochondrial internalization in cardiomyocytes: evidence for rescue of mitochondrial function. Biol Open. (2015) 4:622–6. doi: 10.1242/bio.201511478

198. Hayakawa K, Esposito E, Wang X, Terasaki Y, Liu Y, Xing C, et al. Transfer of mitochondria from astrocytes to neurons after stroke. Nature. (2016) 535:551–5. doi: 10.1038/nature18928

199. Ali Pour P, Hosseinian S, Kheradvar A. Mitochondrial transplantation in cardiomyocytes: foundation, methods, and outcomes. Am J Physiol Cell Physiol. (2021) 321:C489–503. doi: 10.1152/ajpcell.00152.2021

200. Cowan DB, Yao R, Thedsanamoorthy JK, Zurakowski D, del Nido PJ, McCully JD. Transit and fusion of exogenous mitochondria in human heart cells. Nature Sci Rep. (2017) 7:17450. doi: 10.1038/s41598-017-17813-0

201. Zhang TG, Miao CY. Mitochondrial transplantation as a promising therapy for mitochondrial diseases. Acta Pharm Sin B. 2023 Mar;13(3):1028-1035. doi: 10.1016/j.apsb.2022.10.008.

202. Scheiblich H, Dansokho C, Mercan D, Schmidt SV, Bousset L, Wischhof L, Eikens F, Odainic A, Spitzer J, Griep A, Schwartz S, Bano D, Latz E, Melki R, Heneka MT. Microglia jointly degrade fibrillar alpha-synuclein cargo by distribution through tunneling nanotubes. Cell. 2021 Sep 30;184(20):5089-5106.e21. doi: 10.1016/j.cell.2021.09.007

203. Hayakawa K, Esposito E, Wang X, Terasaki Y, Liu Y, Xing C, Ji X, Lo EH. Transfer of mitochondria from astrocytes to neurons after stroke. Nature. 2016 Jul 28;535(7613):551-5. doi: 10.1038/nature18928. Erratum in: Nature. 2016 Sep 14;539(7627):123. PMID: 27466127; PMCID: PMC4968589.

204. Ren, D., Zheng, P., Zou, S. et al. GJA1-20K Enhances Mitochondria Transfer from Astrocytes to Neurons via Cx43-TnTs After Traumatic Brain Injury. Cell Mol Neurobiol 42, 1887–1895 (2022). https://doi.org/10.1007/s10571-021-01070-x