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Dynamic changes of the mitochondria in psychiatric illnesses: new mechanistic insights from human neuronal models

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Abstract

Mitochondria play a crucial role in neuronal function, especially in energy production, generation of reactive oxygen species, and calcium signaling. Multiple lines of evidence have suggested possible involvement of mitochondrial deficits in major psychiatric disorders, such as schizophrenia and bipolar disorder. In the first half, this review will outline the current understanding of the physiological role of mitochondria and their dysfunction under pathological conditions, particularly in psychiatric disorders. Nevertheless, the current knowledge about mitochondrial deficits in these disorders is somewhat limited, due to the lack of effective methods to dissect dynamic changes in the functional deficits that are directly associated with psychiatric conditions. Human neuronal cell model systems, which have been dramatically developed in recent years through the use of stem cell technology, may be key tools for overcoming this dilemma and improving our understanding of the dynamic changes in the mitochondrial deficits in patients with psychiatric disorders. We introduce recent discoveries from new experimental models and conclude the discussion by referring to future perspectives. In the perspectives, we emphasize the significance of combining studies of human neuronal cell models with those of other experimental systems, including animal models.

Keywords

Mitochondria; oxidative stress; calcium dysregulation; human neuronal cell models; Schizophrenia; Bipolar disorder

The mitochondrion is an indispensable organelle of eukaryotic cells that plays many important roles required for cell survival and well-being. It is thought to descend from prokaryotic bacteria through endosymbiotic evolution (1). Neurons are especially dependent on mitochondria, partly because of their high energy demands. As a result, mitochondrial dysfunction leads to multiple types of brain disorders (2–4).

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Mitochondria-associated cellular dysfunction is dynamic, undergoing constant changes in bioenergetics, oxidative stress, and calcium (Ca^{2+}) homeostasis. Thus, it is important to use living model systems to capture their characteristics, relationships, and mechanisms. In this regard, we also need to pay attention to the relevance of each model system to neuronal and brain conditions.

In this review, we first overview current understanding of the mitochondrial functions, in particular: energy production, reactive oxygen species (ROS) generation, and intracellular Ca^{2+} signaling. These elements are interconnected through homeostatic regulation. Next, we shed light on altered mitochondrial function and mitochondrial dynamics under pathological conditions, especially in psychiatric diseases. Nevertheless, the current knowledge in mitochondrial deficits in these disorders is somewhat limited by lack of the effective methods to dissect dynamic changes in mitochondrial function directly associated with patients with psychiatric illnesses. Although studies with the postmortem brains have been essential and informative, living model systems that can recapitulate neuron-relevant signatures have been long awaited.

Recent progress in stem cell biology and cell engineering has answered this question. In contrast to the postmortem brains, which are static and cannot be manipulated, human neuronal cell model systems allow us to study dynamic changes involved in mitochondrial dysfunction. Furthermore, these model systems can be manipulated to address the relationship between pathogenesis and pathophysiology, possibly shedding light on critical mechanisms of the disease pathology. We will introduce various neuronal cell model systems by illustrating unique merits of each model and discuss how they are essential for studying dynamic alteration of mitochondrial functions associated with psychiatric diseases. We will then summarize recent discoveries on the association between mitochondrial dysfunction and major psychiatric illnesses through human neuronal cell models. Lastly, we will provide our perspectives on the value of neuronal cell model systems compared with other model systems.

Physiological roles of mitochondria

At baseline condition, cortical neurons are estimated to consume ~4.7 billion adenosine triphosphate (ATP) molecules/second (5). The site of the highest energy demand is around synapses where ATP is needed for synaptic transmission. The majority of ATP is produced by oxidative phosphorylation in mitochondria, making neurons some of the most metabolically active cells in the body; note that the central nervous system consumes 20% of oxygen at rest while accounting for only 2% of body weight (6). The process of ATP production begins in the cytosol where glucose is converted to pyruvate before transport into mitochondria for oxidative phosphorylation. Mitochondria have both an outer mitochondrial membrane and an inner mitochondrial membrane, creating two separate intracellular compartments: the mitochondrial matrix and the intermembrane space. The outer mitochondrial membrane is permeable to solutes less than 5 kDa whereas the inner mitochondrial membrane is largely impermeable. Enzymes of the tricarboxylic acid (TCA) cycle perform a series of oxidation-reduction reactions within the mitochondrial matrix to provide substrates for the electron transport chain in which energy from electron transport is

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used to pump protons from the matrix into the intermembrane space. The flow of protons back across this gradient is used to drive ATP synthesis by complex V (ATP synthetase). The electrons from the electron transport chain are passed over to O_2 to form H_2O to complete the process. About 1–5% of the electrons passing through the electron transport chain form superoxide (O_2^-) instead of O_2. The O_2^- is converted by superoxide dismutase to H_2O_2, which can form hydroxyl radicals (OH^-). These products form ROS.

Mitochondria are thus the major intracellular source of ROS in neurons. Physiological mitochondrial ROS act as signaling molecules playing a crucial role in healthy cell function and providing metabolic adaptation to mild stress (7). For instance, in growth factor signaling, induction of ROS is needed for downstream tyrosine phosphorylation through inactivation of protein tyrosine phosphatases (8–10). In mitochondria, ROS regulate activity of redox sensitive enzymes and ion channels including Ca^{2+} channels (11). Mitochondria also contain several antioxidant molecules which have been shown to exert neuroprotective effects (12): coenzyme Q10 is a component of the electron transport chain and a potent scavenger of free radicals in the inner mitochondrial membrane; creatine can be converted into phosphocreatine in the mitochondria where it serves as an alternative energy source to ATP and helps maintain the high free energy of ATP; and nicotinamide is the precursor for NADH, the primary substrate for the electron transport chain.

Mitochondria also play a role in Ca^{2+} homeostasis. The organelles contribute to maintain proper intracellular Ca^{2+} levels by functioning together with the endoplasmic reticulum, a major reservoir of the intracellular Ca^{2+} (11,13,14). The outer mitochondrial membrane is Ca^{2+} permeable, allowing Ca^{2+} to be transferred across the inner mitochondrial membrane and the electrical gradient by Ca^{2+} uniporters. High Ca^{2+} concentrations increase activity of the TCA cycle, allowing for increased ATP production necessary for pumping out the increased intracellular Ca^{2+}. This increased ATP production naturally leads to increased levels of ROS. Ca^{2+} inside the mitochondrial matrix can be released through the Na^+/Ca^{2+} exchanger (mNCX), the H^+/Ca^{2+} exchanger (mHCX), and possibly the mitochondrial permeability transition pore (mPTP) (15). Together these channels allow for the rapid shuttling of Ca^{2+} between mitochondria, the endoplasmic reticulum, and the cytosol, coordinating intracellular signaling with energy production. Ca^{2+} influx into subcellular compartments activates Ca^{2+}/CaM-dependent protein kinases and related molecular cascades, which eventually regulate gene transcription underpinning multiple neuronal events (16).

Finally, mitochondria mediate programmed cell death in both physiological contexts during development and pathological conditions (17–19). Both high levels of Ca^{2+} and ROS activate intrinsic apoptotic pathways in the mitochondria, by triggering leakage of pro-apoptotic factors like cytochrome c, apoptosis inducing factor from the mitochondria into the cytosol (18,20). Role for mitochondria-associated programmed cell death in mental illnesses remain elusive.

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Oxidative stress and calcium deficits in the pathology of major mental illnesses: possible involvement of mitochondria

Most psychiatric disorders are caused by multiple etiological factors such as genetic risk factors and environmental stressors (21–25). These multi-factorial etiologies (pathogeneses) likely converge into downstream common pathways in the pathophysiology at the cellular and brain circuitry levels that more directly underlie the symptomatic phenotypes (Figure 1). Within the hierarchical cascades in the pathology, the mitochondrial deficits, such as energy deficits, oxidative stress and redox imbalance, and altered Ca^{2+} homeostasis, are viewed as common pathways in many but not all cases in the pathophysiology of psychiatric diseases (20,26). Although not discussed in this review article, it is also true that many other non-mitochondrial pathways can also contribute to these disorders (24,27,28).

Major deficits in the mitochondria frequently lead to disturbance of energy maintenance. Given the high energy demand of neurons, these defects underlie many brain disorders, in particular neurological disorders, such as neurodegenerative diseases. Because many review articles have covered this topic (mitochondria-associated energy deficits in brain disorders), we cite several representative articles here (29–31) (see a commentary by Ana C. Andreazza in this special issue), and then the remainder of this article will focus on two other deficits associated with mitochondria (oxidative stress and redox imbalance, as well as altered Ca^{2+} homeostasis) and their relationship.

Oxidative stress and redox imbalance

Excess oxidative stress has been reported in patients with mental disorders through studies with peripheral and postmortem brain tissues. Specifically, there is evidence of increased lipid and protein oxidation, together with decreased levels of a major antioxidant, glutathione (GSH), in the blood and cerebrospinal fluid (CSF) of patients with schizophrenia (SZ) and mood disorders (32,33). In addition, several studies have identified a redox imbalance in postmortem brains. For example, the levels of GSH were significantly decreased in the prefrontal cortex of psychiatric patients compared to the control group (34), while nitric oxide species were found increased in striatum from schizophrenic patients (35). There are several studies that tried to assess the levels of GSH in the brain of living patients by magnetic resonance spectroscopy, but the data are not fully conclusive at least at present (36–38).

Parvalbumin interneurons and oligodendrocytes/myelin are the main neural substrates targeted by oxidative stress (39). Several lines of evidence in human postmortem tissues and animal models have suggested that alteration of these two substrates are possibly relevant to the pathophysiology of mental conditions (40–42). Fast spiking parvalbumin interneurons are highly susceptible to oxidative stress because they create high metabolic demand and concomitantly high ROS production (39) Myelination is a biological process that is highly susceptible to oxidative stress: first, myelin is dense in ROS-sensitive lipids; and second, oxidative stress can also affect the process of myelination by disrupting oligodendrocyte maturation (43).

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Oxidative stress is frequently associated with mitochondrial deficits in the brain. As described above, mitochondria are the major source of ROS generation and also contain several antioxidant mechanisms. Compared to other tissues, the risk of redox imbalance is more robust in the brain because of the high lipid content and high metabolic rate, which can be easily translated into high concentrations of lipid peroxides and free radicals (44). Any tissue damage due to oxidative stress is irreversible since neurons are postmitotic cells with no capacity of regeneration (45). Taking all these concepts into account, we can reasonably assume that mitochondria play a significant role in the oxidative stress-related pathophysiology of mental diseases (46). However, we also acknowledge that there are several distinct hypotheses positing that sources other than mitochondria may contribute to high levels of oxidative stress in the brain (46–49). To address the role of mitochondria-associated oxidative stress in the pathophysiology of mental disease, we would need to introduce better models that allow us to recapitulate in finer detail the dynamic mechanisms that lead to excess oxidative stress in neurons. As described below, human neurons *in vitro* obtained from living subjects start to offer this opportunity.

Aberrant $Ca2^{+}$ homeostasis

Pathogenic factors associated with major mental illness could underlie aberrant Ca^{2+} homeostasis in neurons. These factors include genomic abnormalities in the calcium channel genes, which have been shown by genome wide association studies (GWAS) in major mental illnesses. Specifically, GWAS have shown association of SZ, bipolar disorder (BP), major depressive disorder, autism spectrum disorders, and attention deficit-hyperactivity with *CACNA1C* (calcium voltage-gated channel subunit alpha1 C) and *CACNB2* (calcium voltage-gated channel auxiliary subunit beta 2), encoding voltage-dependent L-type calcium channel subunit alpha-1C and beta-2, respectively (50–53). SZ has also been linked to *CACNA1I* (calcium voltage-gated channel subunit alpha1 I), encoding voltage-dependent T-type calcium channel subunit alpha-1I, with genome-wide levels of significance (53).

Excess Ca^{2+} affects both neuronal excitability and signaling cascades regulating gene expression, leading to perturbation of multiple neuronal processes, such as dendrite development, synaptic plasticity, and excitatory/inhibitory balance (16). Altered Ca^{2+} levels in blood cells (red blood cells, neutrophils, T lymphocytes, lymphoblasts, and platelets) have been reported in patients with both SZ and BP. (54–58), Nevertheless, it is unclear whether and how the disease-associated cellular changes in blood cells also occur in neurons and how such Ca^{2+}-related alterations might impact neuronal functions. As Ca^{2+} dynamics cannot be measured in postmortem brain tissue, direct evidence showing abnormal intracellular Ca^{2+} homeostasis is not available within these studies (59).

Ca^{2+} homeostasis and mitochondrial function are directly linked to each other. Increased intracellular Ca^{2+} leads to Ca^{2+} uptake into mitochondria through channels described above. This Ca^{2+} uptake alters mitochondrial membrane permeability and also the electron transport chain efficiency, leading to oxidative stress (60,61). This process creates a reciprocal interaction between mitochondria function/bioenergetics/ROS generation and Ca^{2+} homeostasis, (60,61). Because of this relationship, it would be difficult to study causal relationships between aberrant Ca^{2+} homeostasis and mitochondria dysfunction in a static

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experimental system like postmortem brains; it requires a dynamic and manipulatable experimental platform.

How to study dynamic alteration in the mitochondrial functions associated with psychiatric illnesses: the significance of the use of human neuronal cell models

As described above, mitochondria-associated cellular dysfunction, such as altered bioenergetics, oxidative stress, and Ca^{2+} homeostasis, is dynamic. Thus, it is important to use living model systems to capture their characteristics, relationships, and mechanisms. Progress in stem cell biology and cell engineering has answered this need at least to a reasonable extent: recently developed human neuron model systems have the potential to shed light on dynamic changes involved in mitochondrial dysfunction and could also be manipulated to study the relationship between pathogenesis and pathophysiology.

At present there are at least 4 human neuronal cell models, all of which have advantages and potential limitations in a complementary manner. They are (i) induced pluripotent stem (iPS) cell-derived differentiated neurons (62–65); (ii) induced neuronal cells directly induced from peripheral cells (iN cells) (66–69); (iii) iN cells induced from iPS cells (iPS-iN cells) (70); and (iv) olfactory neuronal cells directly biopsied from the nasal cavity (71–73) (Figure 2).

iPS cells, iN cells, and iPS-iN cells are genetically engineered cells, in which cell reprogramming and conversion technologies with specific sets of transcription factors are utilized. Generating iPS cells is laborious and expensive: furthermore, it takes many months for iPS cell-derived neurons to differentiate and functionally mature. To overcome these issues, iN cells and iPS-iN cells have been introduced. Skin fibroblasts are directly converted into iN cells, bypassing a stem cell stage to generate neuronal cells. iPS-iN cells are generated from iPS cells by bypassing developmental processes with over-expression of exogenously introduced factors. In contrast to these genetically engineered cells, olfactory neuronal cells are directly obtained *via* nasal biopsy and avoid non-specific effects induced by exogenous factors. As each model system has some strengths and weaknesses, these cell models can complement each other in answering specific scientific questions (74). We outline how these cell systems can be complementarily utilized in studying mitochondria-associated parameters in Table 1. Bioenergetics, ROS generation, redox reactions, Ca^{2+} homeostasis, Ca^{2+} -induced excitability, and gene expression profiles have been studied in iPS cell-derived neural progenitors and/or neurons from patients with SZ or BP (75–78). Given their similar properties, iPS-iN cells can also be used for these assays. However, it would not be easy for almost all institutions to establish iPS cells or iPS-iN cells from a large number of patients due to the laborious and expensive nature of generation and maintenance. This fact limits their utility in research for mental disorders in which the majority of cases are sporadic based on the etiology of multiple genetic factors interacting with the environmental stressors (79). iN cells can be established on a larger scale, but they need a purification step before they can be used for biochemical assays or bulk cell/molecular analysis (68,80). Olfactory neuronal cells are a more homogenous population and can be established from a large number of patients, making them fit for high-throughput

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screening assays (81). Although olfactory neuronal cells are of doubtful utility for assessments of excitability, they are reasonably suitable for gene expression analysis since they show similar molecular profiles to stem cells and brain tissues (72).

Recent mitochondria-related findings from human neuronal cell models

In this section, we introduce significant findings in studies that used human-derived neuronal model systems and guided our understanding on the direct contribution of mitochondrial dysfunction, oxidative stress, and aberrant Ca^{2+} homeostasis relevant to the pathophysiology of mental disorders (Table 2). In particular, we highlight studies that showed direct link of the mitochondrial dysfunction and cellular disturbance in patient-derived neuronal cells.

Brennand *et. al.* (82) found excess oxidative stress associated with mitochondrial damage in the iPS cell-derived neural progenitor cells obtained from four patients with SZ as compared to six controls. They investigated potential functional deficits by utilizing a mitochondrial membrane potential (MMP) assay in which the voltage difference across the inner mitochondrial membrane was measured. They observed significantly decreased MMP (indicating mitochondrial dysfunction) in SZ neural progenitor cells relative to control neural progenitor cells, which is the first report that depicts dynamic alteration of the mitochondrial function directly in the neuronal context. Immunohistochemical staining for mitochondrial markers revealed that the mitochondria tended to be smaller, disconnected, and distally distributed in SZ neural progenitor cells, whereas mitochondria in control neural progenitors tended to be more connected, tubular, and highly packed near the perinuclear regions. Importantly, they found more ROS-induced oxidized proteins associated with mitochondria damage in SZ neural progenitor cells, compared to controls. Furthermore, proteomic analysis of these cells also identified disturbances in oxidative stress pathways. Although alteration of oxidative stress-associated molecular disposition in neuronal context had been reported by using olfactory neuronal cells (71), the above mentioned study more directly addressed the dynamics of oxidative stress and mitochondrial deficits. Another group made a case report from iPS cell-derived neural progenitor cells generated from a clozapine resistant SZ patient, in which the same conclusion was drawn (83). The neural progenitor cells from the patient presented a two-fold increase in extra-mitochondrial oxygen consumption together with elevated levels of ROS when compared to cells from a control subject. This difference in ROS levels was reverted by the mood stabilizer valproic acid. Although these studies showed dynamic changes in oxidative stress associated with mitochondrial abnormalities in patients' neuronal cells, the sample size is too small to draw conclusion for mental disorders that are known to be very heterogeneous under the same diagnostic names. Thus, further studies that pay attention to a larger sample size combined with a more sophisticated patient stratification are awaited.

Neuronal hyperexcitability detected by patch-clamp recording and somatic Ca^{2+} imaging linked with mitochondrial abnormalities were reported in hippocampal dentate gyrus granule-cell-like neurons that were differentiated from fibroblast-derived iPS cells obtained from six BP patients, three of whom were lithium responders and three of whom were non-responders (78). Prior to this study, Hahn *et. al.* (84) made a pioneering proposal by using olfactory neuronal cells that indicated an alteration in the Ca^{2+} signaling. By using neurons

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originating from iPS cells, Mertens *et. al.* (78) investigated mitochondrial function by measuring the MMP and found that BP neurons showed higher MMP (enhanced mitochondrial function), a change in line with the upregulated mitochondrial gene expression observed in BP neurons, compared to the control neurons. The BP neurons also had smaller mitochondria than controls. RNA-seq analysis revealed that the pathways involving Ca^{2+} signaling, neuroactive ligand–receptor interaction, and protein kinase PKA/PKC signaling were altered in BP neurons, in addition to changes in the action potential firing system. Using patch-clamp recording and somatic Ca^{2+} imaging, they also observed neuronal hyperexcitability associated with enhanced mitochondrial function in BP neurons. Interestingly, the hyperexcitability was rescued by lithium application in BP neurons from lithium responders, but not in those from non-responders. Taken all together, these results demonstrated direct links between mitochondria abnormalities, aberrant Ca^{2+} signaling, and neuronal hyperexcitability in BP pathophysiology. They also acknowledged that further investigations would be necessary to determine whether mitochondrial alterations represent a cause or a consequence of the observed hyperexcitability phenotype, studies now feasible in human neuron model systems. Notably, this same group also reported hyperexcitability in hippocampal dentate gyrus granule-cell-like neurons differentiated from B lymphoblasts-derived iPS cells of BP patients in an independent cohort (85): this study showed that the cellular abnormalities were rescued by lithium only in the cells from the patients who clinically responded to lithium. We should also note that iPS cells can be generated from multiple types of cells, such as fibroblasts and blood cells. There are discussions on which parent cell type is better suited for studies (86–88): for example, Kyttälä *et. al.* (88) generated iPS cells from two separate sources (fibroblast and blood cells) from multiple individuals, and observed that the individual variability contributes to the iPS cells differentiation potential more than parent cell-type does.

Although they still have some limitations, these studies provide good examples of how human neuronal model systems enable investigation of dynamic changes in mitochondrial function associated with the pathophysiology of the illness. Studies in a larger sample size combined with more sophisticated patient stratification by using multiple, quantitative clinical characteristics are awaited to drive this right direction further.

Perspectives

The study of bioenergetics, oxidative stress, redox signaling, and Ca^{2+} homeostasis can be challenging as they feedback on each other. Postmortem brain studies, functional brain imaging, and genomic studies have been very useful in providing insights into possible links between mental disorders and mitochondrial dysfunction, oxidative stress, and Ca^{2+} homeostasis. However, as far as its dynamic changes are involved, *in vitro* human biopsied neuronal cell models could be a key resource for understanding the mitochondrial dysfunction and its downstream consequences in the patients. Furthermore, by using these models, we can also address whether and how upstream factors including genetic and environmental risk factors affect mitochondrial dysfunction. The potential of using human neuronal cell models in deciphering the hierarchical cascades in the overall pathology is illustrated in Figure 1. Improved techniques using redox sensitive dyes, mitochondrial-targeted probes, and genetically encoded Ca^{2+} indicators enable investigation of these

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dynamic changes in the live cells (Table 1). By using these systems, we can test whether pharmacological and genetic manipulations targeted for specific molecules in mitochondrial bioenergetics, oxidative stress, redox signaling, and/or Ca^{2+} homeostasis could prevent or restore cellular functions (Figure 1). Once we find molecules that could rescue cellular functions, such molecules could be targets for mechanism-based drug discovery research.

Major mental disorders have also been linked to metabolic disorders, which could be intrinsic or developed as a side-effect of medications such as antipsychotics, antidepressants, and mood stabilizers (89–91). Patient-derived cell models could also serve as a valuable resource to tease out the extent of medication or patient-specific factors leading to the pathophysiology, which could ultimately lead to drug discoveries with limited side-effects.

While we have focused primarily on neurons in this review, study of the role of oxidative stress in mental disorders necessarily involves interactions between multiple cell types both within and outside the brain. iPS cell protocols now allow for generation of specific neuronal subtypes as well as astrocytes, oligodendrocytes, and microglia. Human cell lines can thereby be used to study cell autonomous effects in multiple cell types as well as cell-cell interactions between different cell types in co-culture systems. Recently, organoids, miniature functional tissue units, have been generated from human iPS cells through the development of three-dimensional culture systems. Although still in an infant stage of technical development, the experimental system that utilizes organoids would significantly contribute to studying non-cell autonomous effects in normal brain development and brain disorders (92–95).

Nevertheless, *in vitro* systems are limited in their capacity to study the effects of mitochondrial dysfunction across development or at a circuitry level, which is crucial in understanding complex psychiatric disorders. Thus, we propose to utilize human stem cell biology in parallel with proper animal models (96,97) and human brain imaging studies (98). Each experimental system has limitations: we should be very cautious about potential differences between human and animal phenotypes at the circuitry and behavioral levels, and about low spatial and temporal resolution in human brain imaging. However, we optimistically and positively propose that these systems will be able to further identify non-cell autonomous interactions which affect neuronal function and integrate those findings into models of human brain circuitry. In particular, recent studies have highlighted the roles of the immune system, endocrine system, and microbiome in influencing levels of oxidative stress within the brain (28). In summary, studying human neuron cell models complementarily with studying animal models and human brain imaging will clarify dynamic changes in the mitochondrial functions and their mechanisms underlying manifestations of major mental disorders (Table 3).

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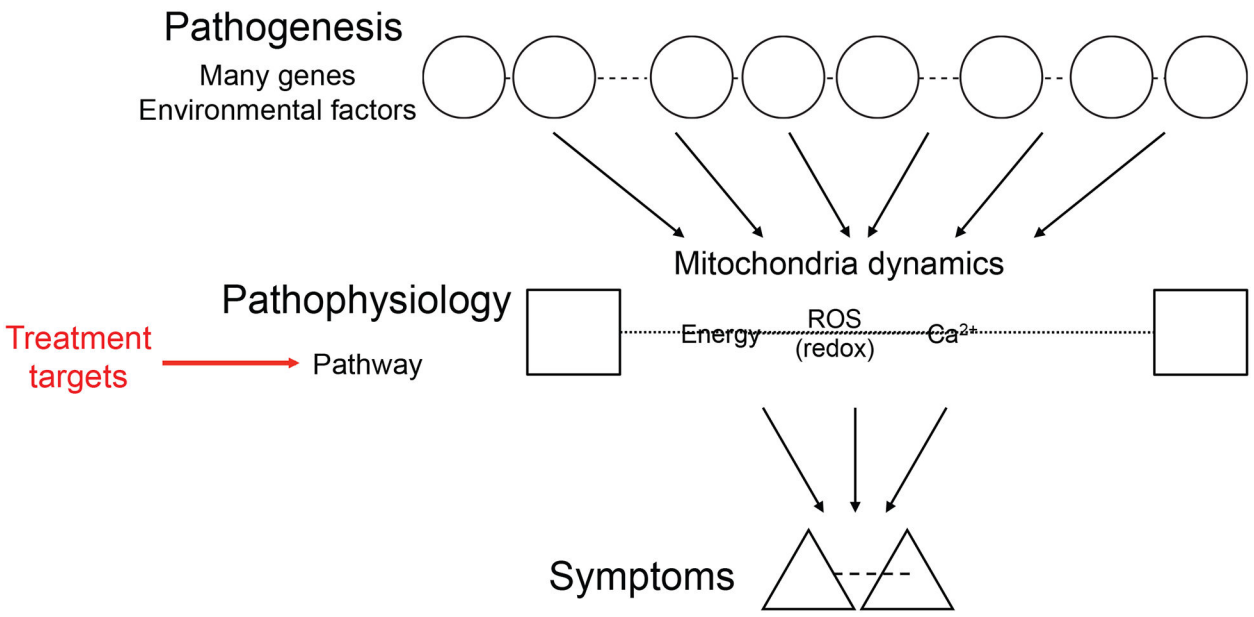

Figure 1: Multiple etiologies (pathogeneses) converging into common pathways (pathophysiology)

In psychiatric diseases, multi-factorial etiological factors such as genetic risk factors and environmental stressors likely converge into downstream common pathways (e.g., mitochondrial deficits leading to energy deficits, oxidative stress and redox imbalance, and altered Ca^{2+} homeostasis). These common pathways (pathophysiology) may underlie the symptomatic phenotypes more directly and are potential targets for course-altering intervention.

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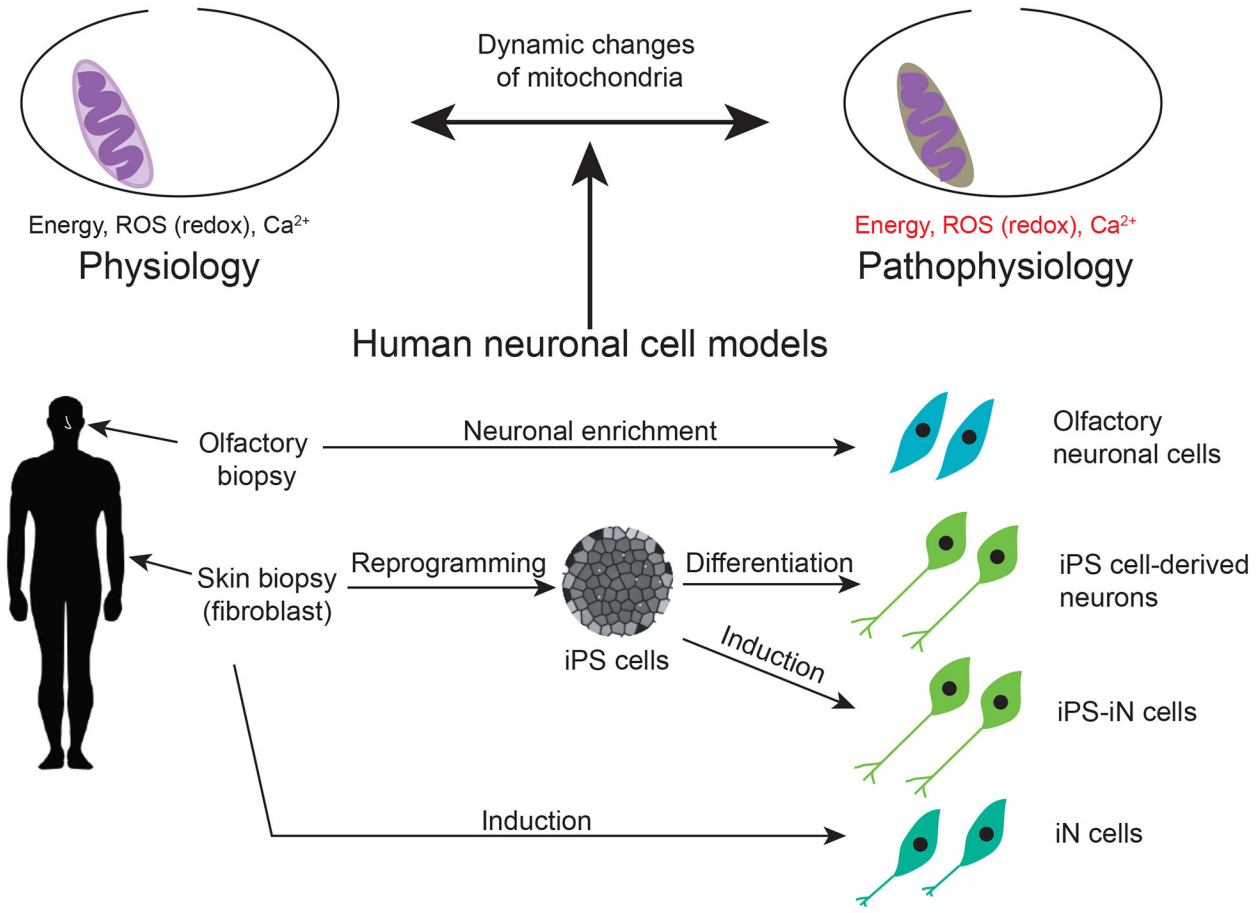

Figure 2: Currently available human neuronal cell models

Four human neuronal cell models are currently available to study dynamics of mitochondrial function and its abnormality.

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Table 1.

Utility of human neuronal cell models in dissecting dynamic alteration in the mitochondrial function associated with psychiatric illnesses

		Bioenergetics	**Oxidative stress**	**Ca^{2+} homeostasis**
Study parameters		Mitochondrial membrane potential, respiration rate, ATP generation	ROS, cellular oxidative stress	Mitochondrial Ca^{2+} basal and stimuli-dependent levels
Techniques widely used		(a) Live cell imaging with fluorescent dye labeling; (b) Seahorse assay	Histology	Fluorescent Ca^{2+} indicators (dyes and genetically encoded indicators)
Reference		77, 78	71, 82, 83, 99, 100	78, 84
Feasibility	**iPSC-derived neurons**	O	O	O
	iPS-iN cells	O	O	O
	iN cells	Cell enrichment is required for (a) and (b)	O	O
	Olfactory neuronal cells	O	O	O

o, theoretically and technically feasible

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Table 2.

Important findings through human neuronal cell models, that might affect mitochondrial function associated with psychiatric illnesses

	Human neuronal cell models	Major findings	Reference
Schizophrenia	Hair follicle-originated iPS cell-derived dopaminergic and glutamatergic neurons	Decreased mitochondrial membrane potential; uneven mitochondrial intracellular distribution	77
	iPS cell-derived neural progenitor cells	Decreased mitochondrial membrane potential; increased levels of ROS	82
		Increased extramitochondrial oxygen consumption and ROS levels. ROS levels reverted by valproic acid	83
	Olfactory neuronal cells	Altered expression and regulation of genes involved in cellular protection against oxidative stress	71
Bipolar disorder	iPS cell-derived hippocampal dentate gyrus granule-cell-like neurons	Altered mitochondrial gene expression, function, size, and Ca^{2+} dynamics (hyperexcitability). Hyperexcitability rescued by lithium in lithium responder, but not in non-lithum responder neurons	78
	B lymphoblasts-originated iPS cell-derived hippocampal dentate gyrus granule-cell-like neurons	Ca^{2+} dynamics (hyperexcitability) rescued by lithium in lithium responder neurons, but not in non-lithum responder neurons	85
	iPS cell-derived neurons	Altered expression levels of calcium channel genes including *CACNA1C* and calcium transients after lithium treatment	101
	Olfactory neuronal cells	Altered Ca^{2+} signaling	84
Subjects with the risk variant for *CACNA1C* (rs1006737)	iN cells	Increased L-type voltage-gated calcium channel current density and expression of *CACNA1C*	102

Unless otherwise noted, iPS cells were derived from skin fibroblasts

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Table 3:

Future perspectives: a multifaceted approach that centers the study of human neuronal cell models

Research domains	Research targets	Suitable research model system/s
Cell autonomous	Cell-specific dynamic changes in mitochondrial bioenergetics, oxidative stress, and Ca^{2+} homeostasis under genetic/environmental manipulations and/or drug treatment	Human neuronal cell models
Non-cell autonomous	Effects of dynamic mitochondrial deficits on interactions among multiple cell types both within and outside the brain	Human neuronal cell models applied to co-culture systems and organoid culture
Circuit	Brain structure/connectivity and clinical manifestations associated with dynamic mitochondrial deficits affected by alterations in the immune system, endocrine system, and microbiome	Human neuronal cell models combined with human brain imaging and/or animal models
Behavior		Human neuronal cell models combined with human clinical evaluations and/or animal models