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Purinergic Signaling and Energy Homeostasis in Psychiatric Disorders

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Abstract

Purinergic signaling regulates numerous vital biological processes in the central nervous system (CNS). The two principle purines, ATP and adenosine act as excitatory and inhibitory neurotransmitters, respectively. Compared to other classical neurotransmitters, the role of purinergic signaling in psychiatric disorders is not well understood or appreciated. Because ATP exerts its main effect on energy homeostasis, neuronal function of ATP has been underestimated. Similarly, adenosine is primarily appreciated as a precursor of nucleotide synthesis during active cell growth and division. However, recent findings suggest that purinergic signaling may explain how neuronal activity is associated neuronal energy charge and energy homeostasis, especially in mental disorders. In this review, we provide an overview of the synaptic function of mitochondria and purines in neuromodulation, synaptic plasticity, and neuron-glia interactions. We summarize how mitochondrial and purinergic dysfunction contribute to mental illnesses such as schizophrenia, bipolar disorder, autism spectrum disorder (ASD), depression, and addiction. Finally, we discuss future implications regarding the pharmacological targeting of mitochondrial and purinergic function for the treatment of psychiatric disorders.

Keywords

Adenosine; ATP; energy homeostasis; mental disorders; mitochondria; glutamate; purine

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

INTRODUCTION

ATP and adenosine are neuromodulatory purines in the central nervous system (CNS). At glutamatergic synapses, ATP is co-secreted into the synaptic cleft, where it modulates synaptic transmission according to the subtypes of purinergic receptors expressed by the presynaptic neuron [1]. ATP may enhance glutamate release through its binding to ionotropic P2X1, P2X3, and P2X7 or inhibit neurotransmitter secretion by binding to presynaptic metabotropic P2Y receptors [2,3]. Synaptic ATP is quickly converted to adenosine through the activity of multiple ectonucleotidases, and additional adenosine can be packaged into synaptic vesicles after degradation of intracellular ATP and secreted as neurotransmitter [1]. This synaptic adenosine acts on four subtypes of adenosine receptors to dampen synaptic activity, reduce neuronal energy consumption, and promote the onset of sleep [1,4,5]. Thus, the extracellular concentration of adenosine acts as an effective indicator of synaptic activity, neuronal energy consumption, and neuronal energy charge that can be sensed by synaptic adenosine receptors to promote neuronal energy conservation and ensure the efficient use of ATP.

In neurons, proper function of mitochondria is essential for the distribution of ATP throughout neuronal subdomains [6–8]. This permits the use of adenine nucleotides for non-energetic purposes such as neuromodulation through purinergic signaling. Thus, proper CNS function is strictly contingent upon the maintenance of active and healthy mitochondria, which in turn regulates the activity of adenine nucleotides, receptors, transporters, and processing of enzymes that participate in neuromodulation. This review will attempt to describe how synaptic dysfunction of mitochondria and the purinergic system often results in severe CNS pathologies, resulting in reduced neuronal health and function which contribute to the development of neuropsychiatric conditions.

MITOCHONDRIA AND ENERGY HOMEOSTASIS

In the CNS, the immense size and cytoplasmic complexity of neurons and glia require mitochondrial integrity and proper distribution in several cellular subdomains. In both cell types, mitochondrial quality is carefully controlled *via* extensive fission and fusion events [9]. The components of aged or dysfunctional mitochondria are frequently recycled through mitophagy and mitochondrial biogenesis [10]. Finally, mitochondrial trafficking along cytoskeletal elements allows for the appropriate distribution of mitochondria and ATP between synapses, axons, and soma. These mechanisms of transport facilitate the retrograde movement required to initiate mitophagic recycling [7,8].

Axonal Transport of Mitochondria

Axons and dendrites as well as astroglial filopodia and lamellopodia, extend significant distances from the cellular soma, thus hindering rapid diffusion of ATP to distal parts of the cell [8]. This necessitates fast and continuous distribution of mitochondria within axons and dendrites in a manner correlating with the energy demands for each individual compartment. Indeed, mitochondria within axons seem to concentrate near boutons en passant, nodes of Ranvier, and axon terminals while those within dendrites localize primarily near

postsynaptic terminals and protein synthesis machinery [11,12]. Mitochondrial trafficking in axons is remarkably discontinuous, as the organelles frequently pause and reverse direction [13,14]. As shown in Fig. (1), these events are instrumental to mitochondrial localization, as these organelles disengage from transport machinery to temporarily reside at locations of high energetic demand [15].

Mitochondrial Dynamics–Fission and Fusion

Ongoing efforts into the understanding of mitochondrial dynamics indicate that the mechanistic relationship of mitochondrial function and trafficking is intrinsically dependent upon mitochondrial fission and fusion [16]. Mutations *via* dominant negative forms of the mitochondrial fission protein dynamin-related protein 1 (Drp1) and the fusion protein Optic atrophy protein 1 (OPA1) reduce mitochondrial content at synaptic terminals and dendritic spines in cultured hippocampal neurons. As a result, these mutations are associated with reduced numbers of synapses and reduced spine density (Fig. 1). While normal axonal mitochondria size ranges between 100 nm to 5 μ m in length, defective mitochondria are extremely long and do not move. This results from defects in mitochondrial fission or fusion, indicating that the dynamic interplay between these states is critical to generate healthy mitochondria suitable for transport [17]. Consequently, transient surges in fission or fusion may be an effective means to regulate mitochondrial transport and the distribution of ATP within neurons and glia.

DIRECT MITOCHONDRIAL CONTRIBUTION TO SYNAPTIC PLASTICITY AND NEURON AND GLIAL FUNCTION

The complex interplay between mitochondrial fission, fusion, transport, and recycling is instrumental for maintaining normal function of mitochondria within neurons and glia. This, in turn, is important for maintaining the integrity of the synaptic environment. Through production of ATP and NAD⁺, healthy mitochondria are essential for the maintenance of phosphorylation reactions and ion homeostasis. Similarly, functioning mitochondria regulates Ca²⁺ signaling via extensive Ca²⁺ buffering which is essential in controlling generation of potentially damaging ROS [18,19]. Furthermore, transient activation of the mitochondria-initiated apoptotic cascade has been implicated in being a direct effector of some forms of synaptic plasticity. For example, inhibition of caspases or overexpression of anti-apoptotic proteins such as X-linked inhibitor of apoptosis protein (XIAP) or the BCL2 family member BCL-XL, prevents AMPA receptor internalization from the postsynaptic membrane and long term depression (LTD). It is interesting that regulation of LTD by these mechanisms are specific to NMDA-receptors, but not metabotropic glutamate receptors, indicating a high level of sensitivity in controlling synaptic plasticity versus apoptosis [20,21].

Purines, such as adenosine and ATP, are both directly and indirectly involved in mitochondrial regulation of synaptic plasticity. P1 and P2 purine receptors are present on both neurons and glial cells of the CNS and perform complex homeostatic functions in both cell types by initiating transient increases in intracellular Ca²⁺ which must be effectively controlled [1,22,23]. Dysfunction in mitochondrial regulation of purinergic mediated Ca²⁺

increases can result in cell death and can adversely affect synaptic plasticity *via* the strengthening or weakening of synaptic connections. Taken together, dysregulation of these mechanisms may contribute to psychiatric disorders such as depression and schizophrenia [18,24,25].

The regulation of synaptic strength is dependent upon the complex interaction of numerous neurotransmitters both at the level of the plasma membrane and mitochondria. Among these neurotransmitters, glutamate and dopamine play an essential role in interacting with neuronal mitochondria and regulate mitochondrial size and transport within the hippocampus [26,27] and forebrain [28]. For example, ionotropic glutamate receptors coordinate Ca^{2+} entry into the postsynaptic terminal and thereby regulate mitochondrial recruitment to postsynaptic domains [26–28]. Furthermore, glutamate-dependent membrane depolarization and Ca^{2+} influx promote Ca^{2+} sequestration within the mitochondrial matrix. This results in depolarization of the mitochondrial membrane, inhibition of mitochondrial transport, and mitochondrial recycling *via* mitophagy in postsynaptic regions [26–28]. Therefore, under normal conditions, glutamate-driven Ca^{2+} uptake significantly contributes both to mitochondrial transport and integrity, potentially promoting the postsynaptic accumulation of mitochondria for Ca^{2+} buffering, until they are eventually recycled [27]. This suggests that glutamate-mediated mitochondrial recruitment and maintenance at the postsynaptic region is vital for the integrity of synaptic strength and health, which is supported by the observation that glutamate toxicity results in neuronal death *via* excessive influx of Ca^{2+} through NMDA glutamate receptors [29].

Similarly, dopamine signaling adversely affects mitochondrial integrity. Dopamine levels are correlated with mitochondrial dysfunctions and play a significant role in dopamine-linked neurological disorders such as Parkinson's disease and schizophrenia [30,31]. For example, in cultured SY5Y cells, dopamine treatment significantly dissipated mitochondrial membrane potential *via* dysregulation of complex I [31]. Thus, impaired efficacy of dopamine uptake may provide one mechanism for mitochondrial dysfunction in schizophrenia [30]. The relationship between purinergic and dopaminergic signaling is of particular importance, as ATP and adenosine appear to have opposing roles in regulating dopamine concentrations within the nucleus accumbens, an area associated with this disorder. For example, delivery of ATP or P2-receptor agonists into the nucleus accumbens increased local concentrations of dopamine, while P2-receptor antagonists and adenosine independently decreased synaptic dopamine within this structure [32]. These results demonstrate an intimate relationship between neuronal activity, dopamine, and purine secretion within the nucleus accumbens [32]. Given the possibility that enhanced dopaminergic signaling can contribute to schizophrenia *via* initiation of mitochondrial dysfunction, defective regulation of dopaminergic and purinergic signaling may also play a role in the progression of other neuropsychiatric disorders. Interestingly, recent work on alcohol use disorders has demonstrated that decreased signaling through A1 and A2A receptors alters downstream CREB function contributing to chronic alcohol consumption and maladaptive compulsive behaviors [33–35]. CREB, an important integrator of dopaminergic and purinergic signaling, plays an important role in neurotransmission and plasticity, both of which are essential in mitochondrial recruitment and integrity at the postsynaptic membrane. Therefore, we may speculate that recruitment and maintenance of

healthy mitochondria is essential to buffer against the oxidative nature of dopamine signaling, as well as the excitotoxic nature of glutamate mediated Ca^{2+} influx.

PURINERGIC SIGNALING

In 1972, Geoffrey Burnstock first hypothesized that ATP and adenosine constitute a class of non-canonical, non-adrenergic, non-cholinergic neurotransmitters [36]. Since then, it has been largely accepted that purines meet the criteria to be designated as neurotransmitters: 1) synthesis and storage in nerve terminals, 2) Ca^{2+} dependent release, 3) synaptic neural responses following exogenous application, 4) inactivation by ecto-enzymes or synaptic re-uptake mechanisms, and 5) inhibition or potentiation of neural responses when exogenously applied [1,37]. Presynaptically located mitochondria permit the local synthesis of ATP, which is subsequently packaged into synaptic vesicles for co-release alongside the canonical neurotransmitters glutamate [38], γ -aminobutyric acid [39], dopamine [32], nor-adrenaline [40], and acetylcholine [40,41]. Alternatively, ATP and adenosine may be released from perisynaptic astrocytes and microglia, *via* glutamatergic co-release and vesicular nucleotide transporter (VNUT)-mediated exocytosis, respectively [42,43]. Synaptic purines from these sources may subsequently act independently or cooperatively to modulate numerous processes including synaptic plasticity, neuroinflammation, and cellular metabolism by binding to a diverse array of purinergic receptors.

As shown in Fig. (2), purinergic receptors are generally classified on the basis of the purine species by which they are activated. ATP and its phosphatebound hydrolysis products, ADP and AMP, activate P2-receptors, while the nucleoside adenosine targets P1-receptors [44]. P1- receptors are G-protein-coupled receptors (GPCRs) that are predominantly located presynaptically in neurons, as well as in astrocytes, microglia, and oligodendrocytes [45]. Conversely, P2-receptors are predominantly located postsynaptically, as well as in astrocytes, microglia, and oligodendrocytes, and are divided into P2X and P2Y subtypes. P2X-receptors are ligand-gated ion channels with varying permeability to K^+ , Na^+ and Ca^{2+} cations [46], while P2Y-receptors are GPCRs coupled to Gs , Gi/o , and Gq/11 [37]. Currently, four subtypes of P1-receptors, seven subtypes of P2X-ionicotropic receptors, and eight subtypes of P2Y-metabotropic receptors have been identified [37]. In the CNS, the P1-metabotropic receptors (A1, A2A, A2B, and A3) activate varying subsets of Gs , Gi/o , and Gq/11 to exert diverse effects on cellular function. A1-receptors bind adenosine to activate Gi/o and inhibit cAMP production, while A2A and A2B receptors increase cAMP by acting through Gs [37]. Interestingly, A3 may activate both Gi/o and Gq/11 , resulting in decreased cellular cAMP and increased concentrations of intracellular inosine-1,4,5- triphosphate (IP3) [47,48].

In contrast to most canonical neurotransmitters, the presence and action of ATP within the synaptic cleft is terminated *via* hydrolysis by extracellular ectonucleotidases, yielding products that serve as additional signaling molecules through activation of purinergic receptors [44]. Interestingly, there is an array of synaptic ectonucleotidases which break down nucleotide triphosphates, diphosphates, and monophosphates that enable the generation of ligands which may act in concert to exert unique synaptic effects [49]. All four major types of ectonucleotidases are found in the brain [158]. Nucleotide specific

ectonucleoside triphosphate diphosphohydrolases (E-NTPDases) target nucleoside tri- and di-phosphates, while ecto-5'-nucleotidases (eN) are specific for mononucleotides [49]. Ectonucleotide pyrophosphatase/phosphodiesterases (E-NPPs) are less specific and degrade nucleoside tri- and diphosphates. Finally, alkaline phosphatases (APs) target tri-, di-, and monophosphates [49]. The products of these enzymatic reactions include nucleoside diphosphates *via* the action of APs, nucleoside monophosphates *via* ENTPDases and APs, inorganic pyrophosphates *via* APs, inorganic phosphate *via* APs, and the nucleoside adenosine *via* degradation of AMP by eN [49]. Each of these products specifically binds and activates a broad array of purinergic receptors on both neurons and glia [1,37,44,49].

Purinergic Signaling and Neuron-Glia Interactions in Neuroinflammation, Synaptic Plasticity, and Cellular Metabolism

Purinergic signaling modulates numerous neurobiological processes, chiefly including neuroinflammation, synaptic plasticity, and energy homeostasis in communicating neurons and glia. Recently, purines have been proposed to act as potent mitokines—purine nucleotides synthesized by mitochondria and released into the extracellular space—which act as signaling molecules for recruitment of immune mediators, during cellular stress (Fig. 2) [50]. This phenomenon has been observed in many tissues including the gut, kidneys, circulatory and skeletal systems. Further, this mechanism of mitochondrial recruitment of immune mediators also exists in neurons of the peripheral and central nervous systems [1,22,23,51,52]. Extracellular ATP is often used as a molecular warning of cellular danger [53]. This promotes vesicular co-release of ATP into extracellular space alongside neurotransmitters, resulting in the recruitment of innate and adaptive immune effectors *via* damage associated molecular patterns (DAMPs) [54–56]. Consequently, chemotactic attraction of neutrophils into the CNS ensues through activation of P2Y2 receptors. Furthermore, activation of resident microglia is initiated as a result of P2X7 and P2Y12 induced elevation of intracellular Ca^{2+} , which can promote neuroinflammation and cell death [57]. Importantly, microglial activation has been associated with numerous neuropsychiatric disorders including depression, schizophrenia, autism, and obsessive-compulsive disorder. For example, animal models of depression induced by chronic psychological stress, repeated social defeat, or learned helplessness display increased numbers of activated microglia. Activation of this cell type has been observed in the prefrontal cortex and hippocampus. Notably, depressive-like behavior and associated microglial activation are reversed by treatment with the antibiotic minocycline [58–60]. Moreover, significant microgliosis and increased expression of the microglia-specific NMDA agonist quinolinic acid have been observed in depressed patients and patients with schizophrenia who succeeded in suicide [61,62]. Interestingly, specific P2X7 variants have also been associated with both bipolar disorder and depression [63,64]. Importantly, P2X7 receptor knockout mice exhibit an antidepressant-like phenotype and higher responsiveness to subtherapeutic doses of the tricyclic antidepressant imipramine [65]. This may place P2X7 as a novel therapeutic target in the treatment of depression and other psychiatric disorders. In addition, it is suggested that microgliosis and increased expression of microglial proteins that affect synaptic transmission, such as quinolinic acid, may contribute to psychiatric disease by modulating the efficacy of synaptic plasticity. However, the specific contribution of P2X7 receptors and microglia activation to the pathophysiology of

psychiatric disorders remains unclear. Thus, purinergic mediated function of this system is extraordinarily complex, and is evident from the differential contribution of neurons, astrocytes, and microglia to synaptic concentrations of ATP, adenosine, and glutamate.

In addition to its role as a neuroinflammatory mitokine, ATP plays an important part in synaptic plasticity and neuron-glia interactions. Glutamate released from presynaptic terminals activates AMPA and NMDA receptors on astrocytes, resulting in rapid Ca^{2+} influx [66]. Interestingly, these astrocytic Ca^{2+} transients have been demonstrated to induce the release of ATP and glutamate through independent as well as co-secretory mechanisms [66–68]. Moreover, synaptic ATP of both neuronal and astroglial origin may activate P2X7 and P2Y1 receptors on astrocyte membranes, resulting in the release of glutamate [69–71]. Both glutamate and ATP also exert complex functions at both the pre- and postsynaptic membranes (Fig. 2). Presynaptically, ATP acts on P2X1, P2X2, P2X3, and P2X4 receptors to enhance neurotransmitter release or on P2Y1, P2Y2 and P2Y4 receptors to inhibit the release of glutamate from presynaptic neurons [3,72]. Postsynaptically, ATP binds both P2X and P2Y receptors to produce transient increases in postsynaptic Ca^{2+} , increasing the efficacy of ion influx through NMDA receptors and resulting in enhancement of synaptic plasticity [73,74]. Synaptic glutamate is not metabolized in the synapse; rather, it is removed from the perisynaptic space by a family of glutamate transporters, including GLT1/EAAT2 [75]. Recovered glutamate can be converted to glutamine and shuttled back the presynaptic terminal [75].

Notably, the high energy demands of neurons and glia dictate that purinergic systems are not the sole source for powering their inherent interactions. As a result, recovered glutamate may enter the TCA cycle to contribute to formation of energy intermediates such as lactic acid [75]. Though lactate production is favored in astrocytes, its breakdown is highly favored in neurons [75]. This may be important for regulating the energy supply for brain circuits that have differential energy demands, largely based on the activity of its constituent cells. Astrocytes may act as a reservoir for energy intermediates, by regulating extracellular levels of lactate and glucose. Interestingly, glutamate uptake potently stimulates glycolysis in astrocytes [76]. Though ATP synthesis *via* mitochondrial oxidative phosphorylation is the principal mechanism of energy production in astrocytes, their unique stellate morphology requires that glycolysis assume a uniquely significant role [77]. This is because astroglial filopodia and lamellopodia, which account for nearly 80% of astrocyte surface area, are frequently too narrow to permit adequate transport of mitochondria [77]. Therefore, these extensions are almost exclusively dependent upon glycogenolysis and glycolysis, as well as passive diffusion, for their supply of ATP [77]. In fact, inhibition of astrocytic glycolysis or glycogenolysis interrupts memory processing and consolidation for bead discrimination in young chickens [78]. Importantly, astroglial GLT1/EAAT2 transporters colocalize with glycolytic enzymes and mitochondrial membrane proteins, suggesting the functional importance between coupling of glutamate and glucose metabolism in astrocytes [79]. ATP and glutamate exhibit co-secretory and reciprocal secretory behavior from astrocytes. However, ATP's role in modulating the secretion and activity of glutamate at presynaptic and postsynaptic membranes, suggests that astroglial energy metabolism heavily influences synaptic plasticity. Furthermore, it is likely that astroglial modulation of synaptic plasticity

is at least partially dependent on glycolytic processes of energy production, namely astroglial secretion of glutamate and ATP, as well as transfer of nutrients to neurons.

Based solely on the information presented above, one may speculate that ATP and glutamate act synergistically to potentiate a positive feedback loop that would, if uninterrupted or unregulated, act to perpetually increase levels of synaptic glutamate and ATP. For instance, the arrival of a train of action potentials is sufficient to depolarize a neuron and initiate glutamate release. Glutamate acts on perisynaptic astrocytes to induce the secretion of additional glutamate and ATP [66–68], which together may act on astrocytes to further increase release of these neurotransmitters. Consequently, this mechanism can act on neurons to induce or inhibit the release of presynaptic glutamate and ATP [47], establishing a positive feedback loop with the propensity to initiate excitotoxic responses. Meanwhile, counterbalancing this system are the degradation of synaptic ATP by ectonucleotidases [49], and removal of glutamate by GLT1/EAAT2. Importantly, synaptic adenosine is effective in counteracting the effects of ATP on astroglial and neuronal receptors. Adenosine's inhibitory function is achieved by, its actions on A1 receptors, resulting in inhibition of presynaptic glutamate release. Additionally, adenosine regulation is critical in control of glutamate-mediated excitatory actions, namely LTP, synaptic activity, plasticity, and NMDA-mediated excitotoxicity (Fig. 3) [80].

Conversely, adenosine's activity at A2A receptors stimulates the release of astroglial glutamate and inhibits astrocytic glutamate uptake by GLT1/EAAT2. It is possible these actions by adenosine offsets its antagonistic role on synaptic concentrations of glutamate and ATP [81,82]. Studies show that deletion of the A2A receptor worsens survival and motor behavior in a transgenic model of Huntington's disease. In line with this, deletion of the A2A receptor worsened white matter lesions and exacerbated cognitive deficits in a mouse model of cerebral ischemia [83,84]. In contrast, A2A receptor blockade prevents synaptotoxicity and memory dysfunction caused by beta-amyloid in mice administered soluble intracerebral amyloid beta peptides [85].

Contribution of Purinergic Signaling on Reward and Addiction Related Disorders

The complexity of purinergic regulation on CNS function also includes reward related mechanisms. Most recently, studies on the A2A receptors has established its involvement in the pathophysiology of addiction. For example, lack of A2A receptors diminish the reinforcing and rewarding properties of cocaine, THC, and nicotine but enhances withdrawal symptoms in mice subjected to morphine addiction [86–89]. Interestingly, A2A and other purinergic receptors have been demonstrated to form both homomeric and heteromeric complexes. Formation of these receptor complexes may augment or inhibit receptor responses depending on receptor constituents. For instance, P2X4 and P2X6 ion channel subunits form a functional and significantly more sensitive ATP-gated channel relative to homomeric P2X4 receptors [90]. Conversely, heteromerization of A1 and A2A receptors, A1 and dopamine D1 receptors, or A2A and dopamine D2 receptors show decreased affinity for their respective ligands [91–93]. Finally, A2A receptors have been demonstrated to dimerize with cannabinoid CB1 receptor and mGluR5 receptors, thus profoundly influencing their respective receptor-ligand affinities [94–96]. Given the promiscuity of

these interactions, purinergic receptors have a significant impact on regulation of the limbic reward processing.

The effect of purinergic regulation is especially evident on the function of the striatum and nucleus accumbens. These structures are critical in modulating the efficacy and duration of endogenous dopamine, cannabinoid, opioid, and glutamate signaling. Moreover, it is likely that the A2A receptor inhibits the synergy in receptor signaling between certain pairs or groups of receptors such as the mu-opioid and CB1 cannabinoid receptors [97]. This represents a likely explanation for the necessity to form a variety of endogenous A2A heterodimers. Specifically, the efficacy, duration, and interaction of numerous neurotransmitters are likely regulated by the formation of A2A heterodimers. By altering the affinity of other receptors, A2A may affect synaptic strength and the inherent neural circuitry. Within the striatum, which frequently involves dopamine and cannabinoid signaling, this may control reward sensitivity and specificity to a variety of addictive or habit-forming stimuli.

The removal of ATP and glutamate from the synaptic system and potential disruptions of the synaptic positive feedback loop can be attributed to three independent processes. As discussed above, regulation occurs through synaptic glutamate removal by astrocytic transporters (GLT1/EAAT2), and glycolytic pathway activation to generate important energy intermediates (lactate) for supplementary energy. A third process by which astrocyte-mediated purinergic signaling maintains synaptic homeostasis is *via* the equilibrative nucleoside transporter ENT1 [98]. Interestingly, glutamate and nucleoside transporters in astrocytes appear to be regulated in tandem, as ENT1- specific antagonists and siRNA reduce EAAT2 expression and glutamate uptake. Conversely, ENT1 overexpression increases the abundance of EAAT2 mRNA in astrocytes [99]. These molecular mechanisms seem to be critical for regulation of addictive related behavior. ENT1-null mice demonstrate an increased preference for ethanol consumption, hypothesized to be due to increased glutamatergic transmission within the nucleus accumbens [33]. Thus, astrocyte energy metabolism may serve an important role in controlling the positive feedback loop that unregulated release of glutamate and ATP can establish. As previously discussed, ATP concentrations may be attenuated by ectonucleotidase mediated degradation into adenosine [49]. In this regard, adenosine may also act *via* astroglial A2A receptors to induce glutamate release, thereby maintaining increased levels of synaptic glutamate [82]. Understanding the inherent complexity of purinergic regulation through adenosine receptor function in an attempt to explain the addiction process is a daunting task. Further complicating this endeavor is the involvement of P2X and P2Y receptors, as well as the relative kinetics of ectonucleotidases [3,72]. Additional studies are warranted to elucidate how the interplay of these components in neurons and astroglia are important determinants in the development of addiction disorders.

Synaptic purines and glutamate may also affect synaptic strength by modulating the activity of perisynaptic microglia. In 2007, Max Bennett published a review postulating the existence of a regenerative synaptic loop at glutamatergic synapses with contributions by astrocytes, neurons, and microglia, responsible for controlling concentrations of synaptic glutamate and purines [100]. He suggested that glutamate-evoked release of ATP from

astrocytes, neurons, and microglia increase synaptic concentrations of purines to act on presynaptic P2X7 receptors. Similarly, synaptic ATP and glutamate act on microglia P2X7 receptors to induce the release of tumor necrosis factor- α (TNF- α), which functions postsynaptically to increase the expression of AMPA receptors [100]. As synaptic ATP and glutamate are maintained by the regenerative loop, they provide sustained release of TNF- α , and continued AMPA receptor enhancement. This increases synaptic efficacy, and contributes to the new functional state of the neural network. During glutamate excitotoxicity, or cytokine mediated inflammatory responses, the regenerative loop may be negatively affected *via* modulation of microglial activity. For example, infections of the CNS activate microglial toll-like receptors (TLRs), which, when combined with the action of P2X7, results in the release of IL-1 β [100]. This anti-inflammatory cytokine acts on postsynaptic neurons to decrease the expression of AMPA receptors and resetting the functional state of the synaptic network [101]. Additionally, cytokines alter the astroglial secretion of neurotrophic factors that exert profound effects on synaptic plasticity and neurogenesis [102]. Taking this into consideration, as well as the fact that P2X7 receptors contribute to the pathophysiology of depression, we may speculate that purinergic signaling can affect the neuroinflammatory response and alter the functionality of neural networks (Table 2). Conversely, there is evidence that decreased functionality of the ATP-glutamate regenerative loop may result in psychiatric illness. For example, a recent report by Cao and colleagues (2013) revealed low ATP levels in the brains of mice subjected to chronic social defeat (Table 2) [103]. Moreover, deficiencies in astrocytic ATP release due to deletion of the type 2 inositol 1,4,5- triphosphate receptor or deficits in astrocytic gliotransmission, caused depressive-like behaviors in mice. These abnormalities were rescued by intracranial administration of ATP, its effects which were mediated by P2X2 receptors within the medial prefrontal cortex. This indicates that region specific synaptic action of ATP on astrocytes and neurons may contribute to the development of psychiatric illness.

Adenosine, provides an effective mechanism of terminating harmful extracellular ATP in tissues [44,104]. The importance of this interplay was quickly evident in studies that examined cellular stress by mechanical shearing, and hyperglutamatergic states [105,106].. Under conditions involving glutamate excitotoxicity there is often an aberrant increase in ATP production. ATP is quickly converted to adenosine by extracellular ectonucleotidases, providing substantial neuroprotection [107]. A similar protective phenomenon can be observed by electron transport chain mediated inhibition of ATP production for the attenuation of hyperalgesia and neuropathic pain [108]. During inflammation, direct cellular damage induces mitochondrial release of formylated peptides, and ATP, both which recruit neutrophils [109,110]. Thus, the accumulation of extracellular ATP promotes inflammatory responses, which is counterbalanced by conversion of ATP to adenosine resulting in protective effects [111–113]. This is particularly observed during ischemic events, where intracellular ATP concentrations decrease to <2nM from normoxic conditions (~3.6nM), thereby promoting the ectonucleotidase degradative pathway. Activation of this pathway favors adenosine generation over inosine-monophosphate and inosine [114], resulting in decreased ATP activity.

Generation of ATP, whether through glycolysis or oxidative phosphorylation, strictly depends on the availability of cofactors, nutrients, and enzymes needed to undergo glycolysis. While enzyme availability is dependent upon cell-autonomous transcription and translation of metabolic proteins, nutrient and cofactor availability are dependent upon the intimate relationship between blood vessels and astrocytes. This essential relationship involves the transport of glucose and lactate, into the brain parenchyma to be used for glycolysis [115]. For example, changes in expression of key astrocyte proteins such as GLUT1 and aquaporin-4 are associated with progression of symptoms in hepatic encephalopathy, a primary astroglialopathy associated with numerous neuropsychiatric symptoms [116]. Under these conditions, decreased transport of glucose and related nutrients into astrocytes leads to inhibition of glucose and lactate shuttling to neurons, thereby crippling neuronal mitochondria and enhancing the production of ROS and nitric oxide. These reactive species enhance the pathological activation of microglia *via* purinergic signaling, which we've discussed is a risk to neuronal health [55]. In addition, there is evidence that the mitochondrial cofactor NADH originating from astrocytes, is essential for prevention of neuronal apoptotic responses. Astrocytes utilize P2X7 receptors to transport NADH across the plasma membrane [117], and neurons subjected to PARP-1-induced genomic instability are rescued when co-cultured with astrocytes and treated with NAD⁺ [118].

Interestingly, changes in mitochondrial bioenergetics and purinergic signaling *via* A1 adenosine receptors have recently been proposed as explanations for the neuroprotective and anti-seizure effects of ketogenic diets [119]. Ketogenic diets limit the availability of glucose as an energy source, thus necessitating the use of ketones for generation of acetyl-CoA and ATP [120]. This utilization of ketones, which are a less efficient substrate for glycolysis, promotes mitochondrial adaptation through increased mitochondrial gene transcription resulting in enhanced mitochondrial biogenesis and bioenergetic efficiency [121]. This increased mitochondrial efficiency promotes rapid turnover of ATP to adenosine, promotes enhanced A1 receptor signaling and subsequent suppression of seizures [122]. Taken together, these data demonstrate that intimate purinergic interactions between astrocytes and neurons are instrumental for neuronal integrity. The extensive crosstalk between the purinergic system and the major excitatory and neuromodulatory neurotransmitters suggests a powerful therapeutic potential, especially in neurological conditions with underlying dysfunction of the neuroimmune response, synaptic plasticity, and neuronal or astrocytic energy metabolism. Additionally, interventions aimed at normalizing the purinergic system may restore normal brain function in individuals with psychiatric illness.

Interestingly, changes in mitochondrial bioenergetics and purinergic signaling *via* A1 adenosine receptors have recently been proposed as explanations for the neuroprotective and anti-seizure effects of ketogenic diets [119]. Ketogenic diets espouse low carbohydrate consumption. This limits the availability of glucose as an energy source, thus necessitating the use of ketones for generation of acetyl-CoA and ATP [120]. This utilization of ketones, which are a less efficient substrate for glycolysis, promotes mitochondrial adaptation *via* increased transcription of mitochondrial genes, thereby enhancing mitochondrial biogenesis and bioenergetic efficiency [121]. This increased mitochondrial efficiency promotes rapid turnover of ATP to adenosine, thereby promoting enhanced signaling *via* P1- A1 receptors

and subsequent suppression of seizures [122]. Taken together, these data demonstrate that intimate purinergic interactions between astrocytes and neurons are instrumental for neuronal integrity. Neuronal secretion of purines and other neurotransmitters allows neurons to convey information regarding their energy status to neighboring astrocytes, influencing glial uptake of glucose and related energy molecules that may subsequently be transferred to neurons. Further, synaptic purines are responsible for the coordinated modulation of glial and neuronal Ca^{2+} currents, modulating the uptake and release of glutamate from both cell types with secondary effects on synaptic plasticity and glutamate toxicity. Finally, because glutamate reuptake and recycling are indirectly dependent upon ATP hydrolysis, synaptic and astrocytic purines play a crucial role in regulating myriad enzymes related to synaptic function and plasticity. This suggests that synaptic activity may transiently decrease ATP concentrations at the presynaptic terminal and perisynaptic astrocytes due to enhanced activation of uptake and recycling molecules as well as binding of presynaptic P1 receptors by ectonuclease-produced adenosine, which may promote astrocytic nutrient uptake to replenish cellular ATP.

Taken together, this data demonstrates the exquisite complexity of purinergic effects on CNS function. Under varying contexts, synaptic purines may assume a neuroinflammatory, neuroprotective, or neuromodulatory role. Furthermore, the extent and quality of neuromodulation appears to be strictly dependent upon the prevalent species of purines and receptors present at the synapse. The differential expression of subunits of the many purinergic receptors may alter their functional characteristics by modulating binding properties of receptors of the purinergic, glutamateric, and dopaminergic systems. This involves the purinergic modulation of dopamine secretion and glutamate recycling. Thus, the extensive crosstalk between the purinergic system and the major excitatory and neuromodulatory neurotransmitters suggests a powerful therapeutic potential for modulation of the purinergic system, especially in neurological conditions with underlying dysfunction in the neuroimmune response, synaptic plasticity, and neuronal or astrocytic energy metabolism. Interventions aimed at normalizing the purinergic system may alleviate dysfunctions in neuroplastic and neuroinflammatory processes restoring normal brain function in individuals with psychiatric illness.

Psychiatric disorders are complex multifactorial conditions likely characterized by dysfunction at the genetic, molecular, cellular, and circuitry levels. An intriguing possibility is that functional disruption in specific neuronal circuits upsets an important balance between numerous parallel circuits that results in cognitive and behavioral abnormalities presenting as psychiatric disorders. Manipulation of the purinergic system within the nucleus accumbens, striatum and medial prefrontal cortex, has profound effects on synaptic transmission and behavior. Importantly, data from animal models of schizophrenia suggest that the modulation of adenosinergic neurotransmission within the nucleus accumbens may be therapeutic for both positive and negative symptoms, significantly improving spatial working memory and social deficits [123,124]. Hence, purinergic signaling plays a unique role in striatal plasticity, as adenosine A2A receptors are enriched in dopamine D2-positive medium spiny neurons in dorsal striatum [125]. In addition to the induction of synaptic plasticity and potentiation by adenosine, these results demonstrate that disruption of striatal function would likely result in severe impairment of striatum-dependent decision making,

evident in neurodegenerative disorders such as Parkinson's disease [126]. Combined, these results suggest complex interactions by synaptic ATP and adenosine, in which synaptic strength, and therefore circuit efficacy, is largely controlled by purinergic mechanisms. This makes it imperative to understand the purinergic involvement underlying development of psychiatric illness.

IN VIVO, GENETIC, AND POST-MORTEM STUDIES OF PATIENTS WITH PSYCHIATRIC DISORDERS

Before proceeding, it is important to note that our discussion of the data reviewed here has focused on purinergic function in CNS physiology and psychiatric disorders. We first outlined details regarding the structure and function of mitochondria, examining how alterations in mitochondrial trafficking, dynamics, and recycling contribute to neuronal and glial dysfunction, which is often correlated in psychiatric disease. As an extension, we mention that mitochondrial dysfunction may lead to spatial or temporal energy homeostatic alterations by over or underproduction of ATP. This lack of energy balance may adversely affect neuronal and glial function by altering cellular or domain-specific energy demands and effectively subjecting cells to oxidative stress. In respect to mitochondrial and bioenergetic dysfunction, this may also affect purinergic signaling, neuroinflammation, and neuroglia metabolism and interactions. However, we would also like to emphasize the extraordinary complexity of purinergic signaling and our limitation in understanding its relation to energy homeostasis within the CNS. While *in vitro* evidence points to malfunctioning mitochondria as culprits in oxidative stress and alterations in bioenergetics, this evidence is derived from isolated systems and may not necessarily reflect *in vivo* conditions. Although animal models are helping us to understand how oxidative stress *via* altered mitochondrial function and bioenergetics contribute to imbalance of ATP to adenosine conversion. Additional mechanistic studies are warranted to safely establish a causative relationship. This is especially evident in human studies, as post mortem and imaging studies offer only snapshots of an increasingly complex interaction between mitochondrial, purinergic and oxidative systems that play a role in psychiatric disorders [127]. Furthermore, it is possible that alterations in purinergic signaling may initiate changes in mitochondrial function, as both of these systems are reliant upon purine synthesis and degradation. Thus, parsing the physiologically spatial and temporal order of events in the discussed pathologies becomes an extraordinarily difficult task. With this caveat in mind, there is increasing evidence that mitochondrial dysfunction and disruption in purinergic signaling occurs in patients and animal models of psychiatric disease. In the following sections we examine and discuss the various avenues of imaging, genetic, pharmacological and post-mortem research supporting dysfunction of purinergic and mitochondrial systems in psychiatric disorders.

Bipolar Disorder

Bipolar disorder (BD) is a chronic, recurrent, heterogeneous, and highly comorbid mental illness. Though the global prevalence approaches only 1% for canonical bipolar disorder I, its frequency could reach nearly 4.4% when including all conditions within the "bipolar spectrum" [128]. As a group, these conditions involve periods of depressive episodes that

alternate with manic (euphoria and impulsivity), hypomanic, or mixed episodes [129], often resulting in higher mortality rates due to suicide and stress-associated cardiovascular disease [130]. Over the past two decades, extensive research has revealed an intricate relationship between mitochondrial dysfunction and BD. Genetic studies have elucidated mitochondrial DNA (mtDNA) abnormalities associated with disease, while functional and imaging studies have demonstrated deficits in mitochondrial function and morphology in patients with BD. The initial hypothesis of mitochondrial dysfunction in BD stemmed from epidemiological studies that demonstrated an increased risk of BD in the offspring of mothers with BD in comparison to offspring of fathers with BD [131]. Though this finding was later challenged by investigations that failed to reveal patterns of maternal mitochondrial inheritance, rare mutations in mtDNA, such as 3243A>G, were found in patients with BD who also exhibit some features of mitochondrial diseases (Table 1) [132]. However, whole genome sequencing of mtDNA of patients with BD has yet to reveal mitochondrial genome variants strongly associated with BD [133]. Still, some mtDNA haplotypes are associated with BD [134] and increased cerebellar pH [133], perhaps providing some clue into the mechanism of neuronal dysfunction in BD. Although the initial studies demonstrating higher levels of mtDNA deletions in brains of patients with BD [135] have not been replicated [136,137], patients with progressive external ophthalmoplegia, a disease manifesting BD and other mood disorders, is associated with mutations in the mitochondrial purine transporter ANT1 (293T>C) (Table 1) [138]. This provides some evidence of the involvement of mtDNA deletion and purine signaling in BD. Overall however, the evidence implicating mutations in mtDNA to BD is astonishingly inconsistent. In addition to mtDNA mutations, abnormalities in gene expression of mitochondria- encoded genes has been found in patients with BD. For example, a recent post-mortem study demonstrated increased expression of the MT-ND1 gene, involved in the mitochondrial electron transport chain, in the brains of patients with BD. Unfortunately, this study failed to find significant correlations between MT-ND1 gene expression and levels of ND1 protein (Table 1) [139]. This may indicate that alterations in expression of genes such as MT-ND1 are compensatory responses to altered processing or translation of transcripts (Table 1). Other studies show that alterations in mitochondria-regulated calcium signaling were observed in patients with BD. For example, in patients with BD, elevated levels of Ca^{2+} are frequently found in peripheral blood platelets and lymphocytes. Moreover, the same was observed in immortalized BD patient lymphoblast cell lines carrying an AA polymorphism. This polymorphism affects B-cell lymphoma-2 expression, and is indicative of endoplasmic astrocytic glucose transport may produce abnormal responses to stress, resulting in maladaptive transcriptional changes promoting aberrant synaptic plasticity.

Mitochondrial structural abnormalities have also been observed in patients with BD. In studies using post-mortem brains, increased numbers of smaller mitochondria were observed in the prefrontal cortex of BD patients compared to controls [146], suggesting that BD may be associated with defective mitochondrial fusion or overactive fission. It is also possible that defective mitophagic responses prevent normal recycling of mitochondria, promoting the accumulation of small, defective mitochondria. In addition, mitochondria are frequently closer to the nucleus in peripheral PBMC of patients with BD compared to controls [146], suggesting defective mitochondrial transport in these patients. A similar defect in neurons

may result in decreased numbers of mitochondria at synaptic terminals, resulting in abnormal synaptic function.

In vivo analyses of mitochondrial function using magnetic resonance spectroscopy (MRS) are also suggestive of mitochondrial abnormalities in patients with BD. For example, brain pH in the frontal lobe is reduced in patients with BD during active episodes and euthymia [147]. Furthermore, two-dimensional proton echo-planar MRS has demonstrated a shift from oxidative to glycolytic energy production during episodes of euthymia, as demonstrated by increased levels of lactate and γ -aminobutyric acid in multiple brain regions [148]. Other markers of mitochondrial function such as ATP, phosphocreatine, and phosphomonoesters have been measured using MRS. These studies show depletion of ATP and phosphocreatine and increased lipid breakdown in the brains of patients with BD [149,150]. In addition, pharmacological treatment in rodent models of mania and BD shows specific enhanced function of mitochondrial respiration, giving further support to the involvement of energy dysregulation in BD. For example, in a transgenic model of BD that accumulates mtDNA mutations (Polg1), Kasahara and colleagues (2006) showed sex specific improvements in circadian-cyclic activity following lithium treatment, but worsened phenotypes with antidepressant exposure [151]. In a subsequent study using DNA microarrays, analysis of postmortem brains of BD patients and Polg1 Tg brains identified the mitochondrial permeability transition pore component cyclophilin-D (CypD) as a potential therapeutic target for BD. Treatment with a CypD inhibitor improved the manic-like behaviors exhibited by Polg1 Tg mice [152]. Similarly, in pharmacologically induced rat models of BD and mania, treatment with lithium, valproic acid and interestingly, tamoxifen, reversed amphetamine and ouabain-induced inhibition of CNS respiratory complexes through a protein kinase-C mediated mechanism [153–155]. In conjunction with these data, the phosphatidylinositol pathway is also involved, as Impa1 and Slc5a3 knockout mice show deficits in mitochondrial oxidative phosphorylation proteins and concomitant BD phenotypes, both of which are normalized following lithium treatment [156].

Mitochondrial dysfunction may also lead to pathological changes in purinergic signaling, which has been implicated in the neurobiology of BD on the basis of its role in behavioral control and its interactions with the dopaminergic and glutamatergic systems. Interestingly, increased plasma levels of uric acid, a metabolite of purine metabolism, were associated with manic episodes and manic symptom severity, but not with the onset or severity of depression or euthymia in a retrospective study of BD I disorder [157]. Similarly, increased levels of uric acid were found in 20 drug-naïve patients who had experienced a first manic episode compared to controls [158]. Several clinical trials have shown that purinergic modulators such as the xanthine oxidase inhibitor allopurinol or the adenosine deaminase inhibitor dipyridamole, used as adjunctive treatment, decrease manic symptomatology [159]. Contradictory evidence has also implicated purinergic receptors such as P2X7 with the pathology of BD. For example, single nucleotide polymorphisms (SNPs) in the P2X7 gene (e.g. rs2230912, A>T resulting in Gln460Arg) are associated with BD and major depressive disorder in large case-control studies [63]. These polymorphisms are also associated with the cognitive symptoms of mania [160], rapid cycling [161], disease course and severity of illness (Table 1) [161,162].

Schizophrenia

Schizophrenia (SZ) is a chronic and highly disabling psychiatric disorder with a global prevalence of approximately 1% and characterized by hallucinations, delusions as well as severe cognitive and social impairments [163]. Although antipsychotics and psychosocial treatments improve some psychotic symptoms, there remains a need for improved treatments for the cognitive and social deficits associated with this disorder. Evidence supporting mitochondrial abnormalities in SZ is limited compared to the evidence elucidated in other mood disorders such as BD. First, there is little evidence supporting maternal mitochondrial inheritance of SZ. For example, in studies of families of SZ patients, no differences between paternal and maternal inheritance rates were found [163]. However, there is evidence of increased odds ratios for inheritance of SZ among relatives of patients with SZ who shared mtDNA [164], providing some inclination that mtDNA inheritance can contribute to SZ. Though studies investigating deletions in mtDNA have found little correlation with the development of SZ [136], a SNP frequently found in mtDNA in brains of patients with SZ (3243A>G), is associated with a decrease in tRNA aminoacylation, a feature found in a mitochondrial disease known as mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) [132]. Thus, while it is unlikely that mtDNA mutations directly contribute to the development of SZ, mitochondrial dysfunction resulting in the development of metabolic conditions may increase the chances of developing SZ. Recent studies show no association between mtDNA SNPs in the NDUF57 gene or haplogroups and SZ [165,166]. However, variations of the gene DISC-1 (disrupted in schizophrenia-1) have been closely associated with SZ (rs751229 A>G and rs3738401 G>A) [167]. Although its exact function is still not well understood, the expression of abnormal DISC-1 in some cell lines results altered mitochondrial dynamics, producing abnormal ring-shaped mitochondria indicative of aberrant fission and fusion (Table 1) [168]. Alternatively, it is possible that the abnormal mitochondrial size and shape frequently observed in SZ patients and in cell lines engineered to express mutant DISC-1 is due to impaired mitochondrial transport, which is intricately linked to fission/fusion dynamics. For example, Atkin and colleagues (2012) recently demonstrated that overexpression of mutant DISC-1 can form protein aggregates that inhibit mitochondrial transport [169]. These results indicate that, though there is little evidence of direct mitochondrial inheritance, there appears to be a correlation between specific SZ risk genes and mitochondrial function. This suggests that disruption of mitochondrial integrity is integral to the pathology of SZ.

Although there is little evidence supporting the existence of mtDNA polymorphisms that contribute to SZ, there is substantially more support for the contribution of polymorphisms in nuclear-encoded mitochondrial genes to SZ pathology. Variations in the upstream region of the complex I gene NDUFV2, including a haplotype consisting of 3542G>A and -602G>A, have been associated with SZ [170]. Similarly, reduction in the expression of several complex I proteins has been reported in patients with SZ. In particular, decreased transcript expression of uncoupling protein-2 (UCP2), involved in the production of reactive oxygen species [171], and decreased NDUFV2 mRNA levels [172] occur in many patients with SZ. Furthermore, decreased activity of complex I (but not complex II and III) was found in 12 patients with SZ compared to matched healthy controls [144]. In contrast, levels of NDUF57 mRNA and complex I activity were unchanged in post-mortem brains of SZ

patients in a different study [143]. Thus, while it is likely that dysfunction of complex I activity and altered expression of nuclear-encoded mitochondrial proteins contributes to the pathology of SZ, it must be appreciated that SZ is a heterogeneous disease resulting from combinations of pathologies that produce the resulting phenotype. It is encouraging that animal studies of SZ have approximated similar findings, which emphasize dopaminergic and glutamatergic regulation of mitochondrial function. Consequently, the dopamine hypothesis of schizophrenia states that increased striatal dopamine and reduced cortical dopamine act together to induce positive symptoms and negative symptoms, respectively [173,174]. Experimental evidence demonstrates that NMDA receptor antagonists such as dizocilpine, phencyclidine, and ketamine induce psychotic symptoms. This can be explained by the glutamate hypothesis which states that hypofunction of glutamate neurocircuitry upstream of striatal dopaminergic structures may be a causative factor in SZ [175]. It is becoming increasingly clear that the apparent overlap in efficacy of mood stabilizers and antipsychotic drugs for the treatment of SZ symptoms is likely due to a common mechanism acting to correct malfunctioning mitochondria, whose dysfunction causes the aberrant release of ATP and an increased release of inflammatory mediators [176,177]. For example, the atypical antipsychotic paliperidone, as well as the mood stabilizers lithium and valproic acid induce increases in expression of synaptic and mitochondrial proteins, promoting mitochondrial migration to the synapse [178,179]. In line with this, administration of the glutamate receptor antagonist ketamine, has recently been shown to specifically affect mitochondrial respiratory chain complexes [180]. Importantly, the atypical antipsychotic clozapine reverses ketamine induced social isolation rearing (SIR) phenotypes and NMDA receptor antagonist dizocilpine induced deficits in pre-pulse inhibition [181–183]. Illustrating these effects, Moller *et al.* (2013) demonstrated how clozapine and N-acetyl cysteine (NAC) reversed SIR induced decreased cortical mitochondrial ATP and increased striatal mitochondrial ATP, while concomitantly alleviating schizophrenia behavioral phenotypes of SIR. These data provide insights as to how clozapine and NAC regulate antioxidant generation *via* glutathione, effectively curtailing mitochondrial generated ROS. These observations provide support for a combinatory role between the dopamine and glutamate hypothesis of schizophrenia. Consequently, purinergic signaling may be a potential bridge between the dopamine and glutamate hypotheses of schizophrenia, since schizophrenia patients treated with atypical antipsychotics show increased adenosine A2A receptor expression. Similarly, adenosine A2A receptor knockout mice, and adenosine kinase transgenic mice display deficient adenosine tone and sensorimotor gating, both of which are ameliorated by increased adenosinergic signaling [123,184,185].

Imaging studies investigating metabolic markers of mitochondrial dysfunction in SZ are limited. However, some MRS investigations have measured brain levels of phosphomonoesters (PMEs) and phosphodiesteres (PMDs) as markers of lipid breakdown and mitochondrial dysfunction. One such study demonstrated temporal lobe metabolism asymmetry showing a higher phosphocreatine to adenosine triphosphate ratio (PCr/ATP) and phosphocreatine/inorganic phosphate ratio (PCr/Pi) in the right as opposed to the left hemisphere [186]. The authors also describe higher levels of ATP in the left hemisphere. A more recent study showed no differences in levels of multiple PMEs and PDEs in the prefrontal cortex of patients with SZ compared to healthy controls [187]. An examination of

the correlation between the N-acetyl-aspartate (NAA)/creatinine ratio (NAA/Cr) and glutamate/glutamine (Glx)/creatinine ratio (Glx/Cr) was measured in the anterior cingulate cortex and hippocampus by ¹H-MRS [188]. The authors reported that the ratios were not significantly different between the SZ and the control group; however a correlation between NAA/Cr and Glx/Cr in the hippocampus of controls was not found in the SZ group, suggesting an uncoupling of these metabolites in the brain of patients with SZ.

Numerous studies have demonstrated a complex interaction between dopamine and ATP. Given the interaction between the purinergic and dopaminergic systems, it is possible that dysfunction of mitochondria or mutation of components of the purinergic system may also play a role in the progression of SZ. Along these lines, SNPs in the adenosine receptors genes have been examined in patients with SZ; twenty-eight SNPs in the A1 receptor gene were investigated yielding a significant association of rs3766553 (in a multivariate analysis) and the SZ phenotype [189]. Conversely, there is no evidence linking A2A receptor gene variations and SZ in German and Taiwanese populations (Table 1) [190,191]. Clinical trials of purinergic modulators (i.e. allopurinol, dipyridamole and propentofylline) have been conducted in patients with SZ. In a recent meta-analysis, treatment with these drugs resulted in significant improvements in the “positive symptoms” (i.e. hallucinations, delusions) and marginally significant improvement in the “negative symptoms” (i.e. social withdrawal), although allopurinol and dipyridamole barely reached statistical significance [159]. Thus, these data indicate that modulation of the purinergic system may be efficacious in the treatment of SZ in concert with classical antipsychotic treatment. It is likely that dysfunction in the purinergic system can result in further abnormalities in both dopaminergic and glutamatergic systems, thereby exacerbating any initial purinergic problem. Therefore, combinatorial treatment of glutamatergic, dopaminergic, and purinergic defects may prove instrumental in the effective treatment of SZ.

Autism Spectrum Disorders—Autism spectrum disorders (ASD) are a group of pervasive and heterogeneous developmental disorders in patients that present with impairments in three major domains: socialization, communication, and behavior. Currently available treatment regimens are insufficient, often leaving patients with ASD severely impaired and unable to work or experience normal social interactions. Interestingly, ASD is closely associated with mitochondrial abnormalities. In fact, the prevalence of abnormal values for molecules, markers, and metabolites indicative of mitochondrial dysfunction is higher in ASD than many other neuropsychiatric conditions. For example, elevated levels of lactate, creatine kinase, ammonia, and pyruvate have been found in peripheral blood in patients with ASD, accompanying decreased levels of total plasma carnitine [192]. Similarly, *in vitro* studies utilizing peripheral blood cells have also revealed abnormalities in mitochondrial function. For example, mitochondrial complex I activity is decreased in lymphocytes of autistic patients compared to controls [193]. Similarly, decreased expression of mitochondrial electron transport chain proteins was found in the cerebellum, temporal lobe, and frontal lobe in post-mortem brains of patients with ASD [194]. As shown in Table 2, increased expression of the mitochondrial fission proteins Fis1 and Drp1 was found during post-mortem evaluation of brain tissue from autistic patients [195]. In addition, the decrease of SOD2 was accompanied by altered expression of proteins responsible for

regulating mitochondrial dynamics. These factors may contribute to the increase in “sick” mitochondria often observed in patients with ASD. The lymphoblastoid mitochondria derived from these patients demonstrate an increased redox ratio of glutathione to oxidized disulfide glutathione [196]. As seen in other psychiatric disorders, genetic variations in mtDNA have been associated with ASD. However, the evidence connecting ASD with specific mtDNA mutations is relatively weak. In one study, only 0.2% of patients with ASD exhibited abnormal levels of mitochondrial tRNA due to a specific mutation in mtDNA (3242A>G) [192]. Furthermore, in a study consisting of 162 parent-proband trios with a diagnosis of autism, there was no association between any of the 10 European mtDNA haplogroups and autism [197] (Table 1). In a similar manner, the role of nuclear-encoded mitochondrial proteins in ASD also remains unclear. In a recent review, Rossignol and colleagues [192] summarized a total of thirteen studies examining the expression of the inner mitochondrial membrane peptidase 2-like gene and the calcium-dependent mitochondrial aspartate-glutamate carrier isoform 1 gene in patients with ASD. They showed that numerous conflicting results make it unclear whether or not the expression of either protein is significantly altered in patients with ASD. Overall, these results speak to the incredibly heterogeneous nature of ASD. It is likely that ASD exists as a true spectrum with members of the population exhibiting extremely heterogeneous symptoms depending on the severity of impairment. However, given the evidence that mitochondrial complexes become impaired in many patients with ASD, it is likely that mitochondrial dysfunction plays a role in the determining the severity of ASD symptomatic presentation.

Neuroimaging has also been utilized to study mitochondrial abnormalities in patients with ASD. One study utilizing MRS reported evidence of decreased cerebellar levels of NAA in children with autism [198]. However, another investigation using ¹H-MRS did not find any significant differences in lactate levels in the anterior commissure and basal ganglia between ASD patients and controls [199]. Thus, evidence linking mitochondrial dysfunction with ASD through the use of MRS remains limited, and future studies should aim to clarify these results. As in BD and SZ, dysregulation of adenosine signaling has been implicated as an underlying mechanism contributing to the pathology of ASD. For example, the ADA2 allele of adenosine deaminase (ADA), which is associated with a hypofunctional enzyme, is associated with ASD (Table 1) in a study of probands with ASD and their unaffected relatives [200]. Similarly, eight SNPs in the A2A adenosine receptor gene were examined in a sample of 98 participants with ASD and 234 controls, showing an association between rs2298383 (C>T) and rs2236624 (T>C) and ASD [201]. Finally, in a recent study of 185 patients with ASD and 305 controls investigating genetic variants and functional correlates the adenosine A3A receptor gene, two rare variants (rs77883500 268C>G and rs139935750 511G>A) exhibited increased cGMP levels when A3A receptors were stimulated with an agonist, while the wild-type did not show increased cGMP levels (Table 1) [202]. Most recently, inhibition of mitokine-mediated purinergic signaling resulted in behavioral and social improvements in a wide spectrum of autism disorders with concomitant recovery of normal synaptic morphology and decreased neuronal cell loss [203]. Furthermore, in a mouse model that lacks a functioning neuronal TSC1/2 and mTOR signaling pathway, continued ER stress engages the intrinsic mitochondrial apoptosis pathway and promotes cell death and neurological impairments, a mechanism linked to autism [204,205]. In

addition, deficiency of the purinergic P2X4 receptor in mice results in deficits in social interaction and sensorimotor gating, behavior phenotypes consistent with autism, thus providing a link to faulty purinergic signaling [206]. Additional mechanistic studies linking the above findings must be conducted in order to gain additional insight into this devastating disease.

Combined, these results support the possibility that mitochondrial dysfunction contributes to the pathophysiology of ASD. Disruptions in mitochondrial dynamics, increased oxidative stress, expression alterations in electron transport chain proteins, and changes in purinergic signaling may combine to create synaptic domains enriched in dysfunctional mitochondria. This in turn, could alter purinergic, glutamatergic, and dopaminergic signaling to adversely affect synaptic activity and plasticity, leading to the formation of the abnormal neural networks which likely contribute to the complex clinical symptoms of ASD.

Major Depressive Disorder—Although the development of major depressive disorder (MDD) is associated with environmental and psychosocial factors, extensive data have demonstrated genetic and molecular alterations in neural tissue of MDD patients. There is abundant evidence of mitochondrial abnormalities in these patients. For example, one study demonstrated that individuals with early onset MDD are significantly more likely to have a mother with MDD than a father with the disorder, thus supporting the possibility of maternal mitochondrial inheritance in MDD *via* mutations in mtDNA [207]. However, evidence of variations in mtDNA in clinical populations with MDD is limited. Copy number of mtDNA in leukocytes of elderly women diagnosed with depression was lower than participants without depression [208]. This suggests that enhancement of mitophagy or mitochondrial fusion, or inhibition of mitochondrial fission, may play a role in the pathology of MDD. This is supported by a recent study demonstrating that a line of Flinders-sensitive rats susceptible to depression contained significantly fewer mitochondria of much larger size within neurons of the CA1 region of the hippocampus. This defect was reversed by treatment with imipramine [209]. In another study, mtDNA deletions were more frequent in MDD patients exhibiting 3 or more somatic symptoms [210]. As a caveat to these findings, we should note that investigations utilizing post-mortem brain tissue from individuals with MDD have failed to reveal differences in activity or expression of components of the electron transport chain [143]. Thus, though it is possible that aberrant mitochondrial dynamics or deletions in mtDNA contribute to MDD, these results should be confirmed in postmortem tissue before therapies targeting mitochondrial function are suggested.

Several studies report that lithium seems to be effective in reducing depression phenotypes induced by chronic mild stress animal models, through regulation of the mitochondrial apoptotic response observed in transgenic mice overexpressing BAG-1 and Bcl-2 [211,212]. Similarly, antidepressant treatment with desipramine, imipramine, and fluoxetine, was shown to upregulate Bcl-2 expression [213–215]. Most recently, Malkesman and colleagues [216] elegantly showed that inhibitory targeting (BI-11A7, BI-11A8, citalopram) of the pro-apoptotic Bcl-2 family member Bid, reduced forced swim test, tail suspension test and learned helplessness depression phenotypes. Taken together, these data highlight how proper mitochondrial regulation of its intrinsic apoptotic pathway can modulate depressive symptoms and consequently pave the way for novel therapeutics.

As an alternative investigational method of energy metabolism, the use of ^{31}P -MRS seems to be an increasingly promising investigational avenue in patients with MDD. In a study involving 35 patients with MDD, the concentration of β -nucleoside triphosphates was significantly lower in the basal ganglia of these patients. However, other high-energy phosphate metabolites were not decreased in these patients [217]. Thus, while it is possible that this change in β -nucleoside triphosphates is caused by alterations in mitochondrial function, it is far more likely that this is a result of altered processing of oxidative synthesized ATP. Such a change in the purinergic system could produce changes in purinergic signaling, possibly resulting in downstream effects on dopaminergic and glutamatergic mechanisms that contribute to the pathology of MDD.

CONCLUSION AND PERSPECTIVE

Energy homeostasis is an essential component for physical and mental health. Recent studies reveal that genetic mutation or malfunction of the genes regulating mitochondrial function may contribute to severe mental disorders in humans. In addition to this, purinergic signaling may play an important role in regulating synaptic activity and promoting normal neuroadaptation. Therefore, dysfunctional mitochondrial structure, subcellular localization and function, as well as improper energy and ATP handling leads to altered purinergic signaling. These maladaptive alterations in CNS function appear to be associated with the aberrant behaviors and thought processes. However, a systems neuroscience approach is required to more fully elucidate the molecular mechanisms underlying dysfunctional energy homeostasis in severe mental disorders. This, in turn, may lead to the development of more precise or specific medications to treat the rapidly increasing numbers of individuals suffering from psychiatric illness

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Biography

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Fig. (1). Overview of the processes of mitochondrial distribution and quality control

Mitochondria synthesized within the soma must be appropriately distributed to neuronal subcellular domains in accordance to the energy demands of each cellular location. Anterograde transport (1) is mediated principally by kinesins (blue), which utilize interactions between the Rho-GTPase Miro (red) and the adaptor protein Milton (green) to anchor mitochondria. Phosphorylation of the light chain of kinesin-1 by GSK3, casein kinase or JNK induces mitochondrial disengagement from transport proteins. Retrograde transport (2) is mediated by cytoplasmic dynein (orange), and plays an equally important role in distributing mitochondria to neuronal subdomains. Importantly, retrograde transport brings dysfunctional mitochondria back to the cell body for recycling by mitophagy (3), a process characterized by deficits in cleavage of PINK1, resulting in recruitment of Parkin and subsequently the autophagy machinery. GSK-3, glycogen synthase kinase-3; JNK, c-Jun N-terminal kinase; PINK1, PTEN-induced putative kinase 1.

Fig. (2). Overview of the major actions of ATP and ADP in the synaptic cleft

ATP is released as a co-transmitter at glutamatergic synapses of the CNS. Similarly, glutamate uptake by astrocytes can promote astrocytic secretion of ATP into the synaptic cleft. Synaptic ATP acts on astrocytes, microglia, and the postsynaptic terminal to exert numerous effects on cellular function. ATP binds to P2X (yellow) and P2Y (green) receptors on astrocytes, promoting the release of Ca^{2+} from mitochondria. This subsequently results in depolarization of the mitochondrial membrane and an increase in ROS production. Further, Ca^{2+} transients generated by ATP binding at astrocytes can result in transcriptional changes that temporarily alter astrocyte function. Postsynaptically, ATP binds both P2X and P2Y receptors to produce transient increases in postsynaptic Ca^{2+} , increasing the efficacy of ion influx through NMDA receptors and resulting in enhancement of synaptic plasticity. Synaptic ATP can also act on surrounding microglia. In this instance, ATP signals primarily through P2Y receptors and acts as a cellular danger signal, activating microglia and promoting neuroinflammation. Synaptic ATP is rapidly converted to adenosine (ADO) by

ectonucleotidases. ADO binds presynaptic P1 (blue) receptors to inhibit the release of neurotransmitter from the presynaptic terminal. Alternatively, ADO may act postsynaptically by decreasing the efficiency of ion influx through AMPA and NMDA receptors (red). Importantly, ADO may also act on neighboring microglia, where its signaling through P1 receptors inhibits their conversion to a reactive phenotype, thus inhibiting the action of ATP on microglial activation.

Fig. (3). Overview of the metabolic relationship between astrocytes and neurons

Nutrient flow between astrocytes and neurons is instrumental for neuronal health. At glutamatergic synapses, 90% of glutamate reuptake is mediated by astrocyte EAAT1/2 transporters. Within astrocytes, glutamate may either enter the TCA cycle or be converted to glutamine. Importantly, lactate production is highly favored in astrocytes, while its breakdown is favored in neurons. Glutamine and lactate are subsequently shuttled to neurons, where glutamine is converted to glutamate and lactate may be degraded for ATP production. Astrocytes are integral for CNS blood brain barrier permeability of glucose and NADH, mediated through GLUT1 and P2X7. NADH can be directly shuttled to neurons to

contribute to ATP production. Disruption of this system may contribute to the neuronal metabolic dysfunction that is manifested in psychiatric disease.

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Table 1

Genetic variants of the genes of energy homeostasis and purine signaling.

Mutation/SNP	Location	Associated Protein/RNA	Disorders	Reference(s)
3243A>G	Mitochondria	MT-TL1 (Mitochondrial leucine-carrying tRNA)	BD SZ	[132]
12358A>G	Mitochondria	MT-ND5 (Complex I)	BD	[139]
4977 bp deletion	Mitochondria	MT-ND1 and MT-ND4 (Complex I)	BD	[137,139]
ANT1 293T>C	Nuclear	ANT1 (Mitochondrial purine transporter)	BD	[138]
rs4765913 CACNA1C A>T	Nuclear	CaV1.2 (alpha subunit of voltage-gated L-type Ca ²⁺ channel)	BD	[222]
rs2230912:A>G	Nuclear	P2X7 (Purine receptor)	BD, MDD	[63]
rs751229:A>G rs3738401:G>A	Nuclear	DISC1 mitochondrial transport mitochondrial dynamics	SZ	[167,168]
3542G>A 602G>A	Nuclear	NDUFV2 (Mitochondria complex I flavoprotein)	SZ	[170]
rs3766553:C>T	Nuclear	Adenosine A1 receptor	SZ	[189–191]
3242A>G	Mitochondria	MT-TL1 (Mitochondrial leucine-carrying tRNA)	ASD	[192,197]
ADA2 adenosine deaminase allele	Nuclear	Adenosine deaminase	ASD	[200]
rs2298383:C>T rs2236624:T>C	Nuclear	Adenosine A2A receptor	ASD	[201]
rs77883500:268C>G rs139935750:511G>A	Nuclear	Adenosine A3 receptor	ASD	[202]

Table 2

Mutant and deleted proteins of the purinergic or mitochondrial system associated with psychiatric and neurological disease in animal models.

Genes	Phenotypes	Disorders	References
Drp1	Reduced mitochondrial content at synaptic spines and terminals;	ASD	[17,195]
OPA1	Reduced mitochondrial content at synaptic spines and terminals;	ASD	[17,195]
P2X7	Antidepressant-like effect in: forced swim test, tail suspension test. Enhanced response to subtherapeutic doses of antidepressants	BD, MDD	[63–65]
A2A Receptor	Impaired survival and motor function in model of Huntington's disease; White matter lesions and cognitive deficits associated with hypoperfusion; Diminished rewarding effects of many drugs	Alcoholism Ischemia	[35,83,84,86–88]
ENT1	Decreased expression of glutamate transporter EAAT2; increased preference for ethanol consumption	Alcoholism	[33,99]
P2X2	Associated with the antidepressant-like effects of synaptic ATP	MDD	[103]