Molecules and Cells

Minireview

Proline Metabolism in Neurological and Psychiatric Disorders

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Proline plays a multifaceted role in protein synthesis, redox balance, cell fate regulation, brain development, and other cellular and physiological processes. Here, we focus our review on proline metabolism in neurons, highlighting the role of dysregulated proline metabolism in neuronal dysfunction and consequently neurological and psychiatric disorders. We will discuss the association between genetic and protein function of enzymes in the proline pathway and the development of neurological and psychiatric disorders. We will conclude with a potential mechanism of proline metabolism in neuronal function and mental health.

Keywords: cell metabolism, neurological disease, neuron, proline, psychiatric disease

INTRODUCTION

The prevalence of neurological and psychiatric disorders was approximately 1.28 billion as of 2017, accounting for 17.4% of the global disease burden (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). psychiatric disorders frequently accompany neurological disorders, e.g., Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy, migraine, essential tremors, and stroke (Kupeli et al., 2021). Both neurological and psychiatric disorders are associated with impaired neurotransmission, altered brain structure, inflammation, and impaired neurotrophic signaling (Kupeli et al., 2021). Treatments targeting these abnormalities appear to be effective but with significant adverse side effects, and more efficacious therapies for neurological and psychiatric disorders remain an unmet need.

In this review, we focus on the nonessential amino acid proline, the accumulation of which leads to hyperprolinemia. As early as 1989, a hyperprolinemia patient's brain showed a low density of white matter (Steinlin et al., 1989), which indicates a potential role of proline metabolism in neuronal morphology and function.

NEURONAL METABOLISM

Glucose is the primary substrate of neuronal metabolism. Neuronal cells take up glucose through specific glucose transporters, which are then phosphorylated by hexokinase to produce glucose-6-phosphate (Dienel, 2019). Glucose-6-phosphate goes through different metabolic pathways and eventually becomes oxidized to CO₂ and H₂O in the brain (Dienel, 2019). However, as glucose can follow different metabolic routes, each neuron does not necessarily metabolize glucose to produce CO₂ and H₂O (Zielke et al., 2009). Indeed, glucose can form a wide range of metabolic intermediates, such as lactate, pyruvate, glutamate, and acetate, in neurons. These intermediates can subsequently be oxidized for energy production, serve as neurotransmitters and so on (Zielke et al., 2009). Damage to these processes can lead to neurological disturbances, loss of consciousness, and even coma within...
Lipids comprise approximately 50% of the brain’s dry weight. They are the key components that support the brain’s complex structure and function (Barber and Raben, 2019). It has long been known that lipid component fatty acids can enter the brain and be oxidized (Allweis et al., 1966; Dhopheshwarkar and Mead, 1970). There is evidence that approximately 20% of the total energy expenditure of the adult brain is provided by the oxidation of fatty acids (Ebert et al., 2003). Moreover, long-chain polyunsaturated fatty acids (PUFAs) have been proven to be the precursors of several metabolites with different effects on inflammation and neuron outgrowth (Martinat et al., 2021). Omega-3, a PUFA, is a potential treatment for schizophrenia (Frajerman et al., 2021). Except for the fatty acid itself, a few lipid metabolism enzymes have been identified at synaptic terminals, where they can locally modulate synaptic transmission (Di Paolo et al., 2004; Rohrbough et al., 2004). Unlike adipocytes and liver cells, neurons are not energy-storage cells. Thus, they do not normally contain significant amounts of nonstructural lipids and receive metabolites oxidized from fatty acids, such as ketones, NADH, acetyl-CoA, and FADH, from astrocytes (Barber and Raben, 2019).

Amino acids are better known for their roles in producing neurotransmitters than providing energy. Glutamate is the most abundant amino acid in the mammalian brain and functions as an excitatory neurotransmitter (Clark and Amara, 1993). Aspartate was later identified as an excitatory neurotransmitter (D’Aniello et al., 2011). γ-Aminobutyric acid (GABA) and glycine are inhibitory neurotransmitters (Clark and Amara, 1993). Except for these amino acids that serve as neurotransmitters, the functions of the other amino acids, such as proline, are less well understood. It is interesting to note that accumulating evidence now indicates that proline is associated with neurological and psychiatric disorders (Mayneris-Perxachs et al., 2022; Mitsubuchi et al., 2014).

Most nutrient metabolism occurs in the mitochondria, the powerhouse of the cell. Mitochondria are highly dynamic organelles that divide, fuse, and move purposefully within axons and dendrites (Mattson et al., 2008). In neurons, mitochondria are the major sites for energy production, generation of reactive oxygen species (ROS), calcium signaling, developmental and synaptic plasticity, and the arbitration of cell survival and death (Srivistava et al., 2018). Many gene products are localized in the mitochondria, and mutations of these genes have been linked to neurological and psychiatric diseases (Franco et al., 2021; Iwamoto et al., 2005; Sreedharan et al., 2008). Mitochondria-mediated oxidative stress perturbs Ca2+ homeostasis, and apoptosis also contributes to the pathogenesis of prominent neurological diseases, including AD, PD, Huntington’s disease, stroke, amyotrophic lateral sclerosis (ALS), and psychiatric disorders (Chan, 2020; Falabella et al., 2021). Overall, nutrient metabolism in mitochondria has a profound effect on neuronal functions, and prolonged defects eventually lead to neurological and psychiatric disorders (Fig. 1).

Fig. 1. Overview of proline metabolism in neurological and psychiatric disorders.
NEURONAL DYSFUNCTION IN NEUROLOGICAL AND PSYCHIATRIC DISORDERS

AD is the most common neurodegenerative disorder and the leading cause of dementia in the elderly (Palop and Mucke, 2010). The hallmark of AD is the accumulation of pathogenic amyloid-β (Aβ) assemblies in the brain, resulting in the progressive dismantling of synapses, neuronal circuits, and networks (Querfurth and LaFerla, 2010). In AD patients, hippocampal synapses begin to decline, and synaptic profiles show compensatory increases in size. They also show a reduction of approximately 25% in the presynaptic vesicle protein synaptophysin (Querfurth and LaFerla, 2010). Moreover, abnormal axons associated with neurofibrillary tangles and abnormal thin and tortuous axons were shown in patients’ brains (Stokin and Goldstein, 2006). In vitro studies showed that elevated Aβ attenuates excitatory synaptic transmission by decreasing the number of surface AMPA receptors and NMDA receptors, which is associated with a collapse of glutamatergic dendritic spines (Hsieh et al., 2006; Shankar et al., 2007).

PD is a progressive neurodegenerative disease that affects 2%-3% of the population ≥65 years of age (Poewe et al., 2017). The main neuropathological hallmarks of PD are dopaminergic neuronal loss in the pars compacta of the substantia nigra (SNc) and accumulation of intraneuronal inclusions called Lewy bodies and Lewy neurites (Calabresi et al., 2013). However, it is not clear what causes the death of dopaminergic neurons. One hypothesis is that accumulated mitochondrial DNA damage produced by ROS and related free radicals generated in oxidative phosphorylation would lead to the dysfunction of Ca<sup>2+</sup> channels for pacemaking. SNc dopamine neuron activity relies on Ca<sup>2+</sup> channels. This reliance may cause persistent metabolic stress on mitochondria, accelerating SNc dopamine neuron aging and death (Surmeier, 2007). In addition to the Ca<sup>2+</sup> channel and mitochondrial hypothesis, new insights have suggested that inflammation causes brain blood barrier dysfunctions and gut-brain connections (Bartels et al., 2020; Sweeney et al., 2019; Travagli et al., 2020).

Schizophrenia is a severe psychiatric disorder that has a profound impact on the individual and society (Owen et al., 2016). Diagnosis is made clinically based on history and mental status examination. There are no diagnostic tests or biomarkers (Owen et al., 2016). However, one of the most consistent findings in schizophrenia is ventricular enlargement and decreased brain volume involving the hippocampus and cortex (Bellon, 2007). There are many hypotheses for schizophrenia. The first is the dopamine hypothesis. Several clinical studies reported that schizophrenia patients showed elevated presynaptic striatal dopamine synthesis, while other studies reported either a small but not significant elevation or a small reduction in dopamine levels (Howes and Kapur, 2009). On the other hand, dopamine receptors also showed abnormal expression; however, studies were inconsistent (Howes and Kapur, 2009). The second is the glutamate hypothesis. In addition to NMDAR antagonist studies, brain imaging studies, and genetic studies, postmortem studies are the most direct evidence. In patients, postmortem studies revealed a significant reduction in GABA levels in the prefrontal cortex, a reduced number of GAD67-expressing neurons that coexpress NR2A in the prefrontal cortex, and reduced activity of glutamate carboxypeptidase II in the frontal cortex, hippocampus, and temporal cortex (Coyle, 2006; Uno and Coyle, 2019). Other hypotheses, such as serotonin, inflammation and two-hits, have also been proposed (Eggers, 2013; Feigenson et al., 2014). More evidence and clear hypotheses are needed for the diagnosis and treatment of schizophrenia.

PROLINE METABOLISM IN NEUROLOGICAL AND PSYCHIATRIC DISORDERS

Proline is a nonessential amino acid involved in adaptation to osmotic and dehydration stresses, redox control, and apoptosis (Fichman et al., 2015). Proline is catabolized to pyroline-5-carboxylate (P5C) by proline dehydrogenase (PRODH) in the mitochondrial matrix, generating glutamate through NAD-dependent P5C dehydrogenase (P5CDH). Glutamate is an important excitatory neurotransmitter in neurons and a precursor to glutamine, GABA and mitochondrial TCA cycle intermediates. Conversely, glutamate is converted into a P5C intermediate through P5C synthase (P5CS) and further reduced to proline by P5C reductases (PYCRs). All of the enzymes in the proline metabolism pathway have been reported to be associated with neurological or psychiatric disorders in human and animal models (Table 1) (Guo et al., 2018; Li et al., 2021; Liu et al., 2009).

A high-throughput metabolomics study reported that proline metabolism plays a key role in the progression from healthy to mild cognitive impairment to AD in a natural aging population (Xie et al., 2021). The disease-metabolite-pathway associations highlight the importance of proline in all three neurodegenerative diseases, including AD, PD, and ALS (Kori et al., 2016). Clinically, patients with P5CS deficiency present profound manifestations with progressive neurodegeneration, mental retardation, peripheral neuropathy, joint laxity and cataracts (Baumgartner et al., 2000; Phang et al., 2013). Twenty-four hypomethylating leukodystrophy patients with mutations in the proline synthase gene, PYCR2, displayed postnatal progressive microcephaly, poor overall growth, and severely delayed psychomotor development. Neuroimaging analysis of these patients revealed a decreased myelin sheath, thinning of the corpus callosum and brainstem, and a general decrease in white matter volume (Escande-Beillard et al., 2020). The proline-degrading enzyme PRODH is located on chromosome 22q11, a schizophrenia locus. At least eight single nucleotide polymorphisms have been reported in the PRODH gene in patients with schizophrenia (Bender et al., 2005; de Koning et al., 2015; Ota et al., 2014), and one hyperprolinemia patient was found to have white matter abnormalities (Steinlin et al., 1989). Interestingly, hydroxyproline and proline concentrations in urine are influenced by stress and anxiety (Lee et al., 2011).

In animal models, Pycr2 knockout mice developed progressive neurological symptoms, including white matter defects, marked developmental delay, and premature death (Escande-Beillard et al., 2020). Glutamate, GABA and aspartate were significantly reduced in the hypothalamus and frontal
Table 1. Proline metabolism in diseases

| Gene/enzyme names | Type of mutations | Disease/phenotype | References |
|-------------------|-------------------|-------------------|------------|
| P5CS              | Deletion          | Progressive neurodegeneration | (Baumgartner et al., 2000) |
|                   |                   | Mental retardation | (Baumgartner et al., 2000) |
|                   |                   | Peripheral neuropathy | (Baumgartner et al., 2000) |
|                   |                   | Joint laxity | (Baumgartner et al., 2000) |
|                   |                   | Cataract | (Baumgartner et al., 2000) |
| PYCR2             | Mutation          | Microcephaly | (Escande-Beillard et al., 2020) |
|                   |                   | Hypomyelination | (Escande-Beillard et al., 2020) |
|                   |                   | Poor overall growth | (Escande-Beillard et al., 2020) |
|                   |                   | Delayed psychomotor development | (Escande-Beillard et al., 2020) |
| PYCR1             | Overexpression    | Liver cancer | (Li et al., 2021) |
|                   | Deletion          | ARCL2 | (Guernsey et al., 2009) |
|                   | Overexpression    | Lung cancer | (Li et al., 2021) |
|                   |                   | Hepatocellular carcinoma | (Li et al., 2021) |
|                   |                   | Colorectal cancer | (Li et al., 2021) |
|                   |                   | Gastric cancer | (Li et al., 2021) |
|                   |                   | Breast cancer | (Li et al., 2021) |
|                   |                   | Prostate cancer | (Li et al., 2021) |
|                   |                   | Bladder cancer | (Li et al., 2021) |
|                   |                   | Esophagus cancer | (Li et al., 2021) |
|                   |                   | Gliomas | (Li et al., 2021) |
| PRODH             | Mutation          | Schizophrenia | (de Koning et al., 2015) |
|                   |                   | HPI | (Mitsubuchi et al., 2014) |
| P5CDH             | Reduced expression | Colorectal cancer | (Liu et al., 2009) |
|                   | Deficiency        | HPII | (Mitsubuchi et al., 2014) |

HPII is that in the hypothalamus, proline is taken up by astrocytes. Then, proline is converted into lactate, which is then released from astrocytes and taken up by neurons. In neurons, lactate is oxidized for energy production (Arrieta-Cruz and Gutierrez-Juarez, 2016). However, direct evidence is still lacking for a causal role of proline metabolism in nonneuronal cells in the development of neurological and psychiatric diseases.

PROLINE METABOLISM IN OTHER DISEASES

Proline metabolism has been implicated in neurological and psychiatric disorders as well as in other diseases (Table 1). Accumulation of proline can lead to hyperprolinemia due to the dysfunction of catabolic enzymes. There are two types of hyperprolinemia: type I (HPI) and type II (HPII). They are both caused by inborn errors of the proline metabolic pathway (Mitsubuchi et al., 2014). HPI is caused by an abnormality in the PRODH gene, while HPII is caused by a deficiency of the P5CDH gene. The clinical features of HPI are unclear. Nephropathy, uncontrolled seizures, mental retardation and schizophrenia have been reported in HPI, but a benign phenotype without neurological problems has also been reported (Mitsubuchi et al., 2014). PYCRs are also linked to many human diseases. A missense mutation in PYCR1 was found to cause autosomal-recessive cutis laxa type 2 (ARCL2), a multisystem disorder including premature aging, wrinkled and lax skin, joint laxity, and developmental delay (Guernsey et al., 2009). Two homozygous mutations in PYCR2 have been reported to cause microcephaly and hypomyelination, suggesting a crucial role of PYCR2 in the development of the human nervous system (Nakayama et al., 2015).

Dysregulation in proline metabolism is also broadly observed in cancer. PYCRs play an indispensable role in promoting tumorigenesis and cancer progression, and they are...
upregulated in many different cancer types, including lung, liver, colorectal, gastric, breast, prostate, bladder, gliomas and esophageal cancer (Li et al., 2021). In breast cancer, PYCR1 but not PYCR2 was also correlated with poor survival (Ding et al., 2017). In contrast, PRODH is a tumor suppressor. PRODH expression levels were much lower in tumor tissues when compared to normal tissues (Liu et al., 2009). When PRODH was inhibited, tumors were readily formed in human colon xenograft animal models. When PRODH was overexpressed, tumors were either suppressed or were so small that the animals did not require euthanasia (Liu et al., 2009).

**MOLECULAR EVENTS ASSOCIATED WITH PROLINE METABOLISM**

Proline is not only an essential component of proteins but also plays an important role in adaptation to osmotic and dehydration stresses, redox control, and apoptosis. The proline metabolism pathway is conserved in a variety of organisms, e.g., from bacteria to plants and humans (Fichman et al., 2015).

Numerous studies have linked proline metabolism with ROS (Liang et al., 2013). On the one hand, proline acts as an ROS scavenger. For example, in cultured skin fibroblasts, exogenous addition of proline diminished singlet oxygen (¹O₂) levels (Wondrak et al., 2005). Moreover, proline can protect human skin cells from photoinduced apoptosis, suggesting that proline can suppress photocytotoxicity and skin carcinogenesis (Wondrak et al., 2005). In plants, the production of ¹O₂ in the thylakoids from the cotyledons of Brassica juncea was dramatically suppressed by proline under strong illumination (Ala et al., 1997). On the other hand, proline metabolism may also lead to increased endogenous ROS (Liu et al., 2012; Szabados and Savoure, 2010; Zarse et al., 2012). In mammalian cells, PRODH activity increases mitochondrial ROS production (Liu et al., 2006). PRODH is a p53-inducible gene (Nagano et al., 2017). Upregulation of PRODH by p53 increases mitochondrial superoxide (O₂⁻↓) production, leading to cytochrome c release and caspase-9 activation (Hu et al., 2007). Elevated ROS levels induced by PRODH have also been associated with the activation of apoptotic pathways via the Ca²⁺/calcineurin-NFAT cascade (Liu et al., 2006). PRODH is activated by peroxisome proliferator-activated receptor γ (PPARγ), where PRODH-dependent ROS are important mediators of apoptosis in cancer cells treated with PPARγ ligands (Pandhare et al., 2006; Zou et al., 2007). Overall, proline and proline metabolism can act as both an ROS scavenger and producer. Therefore, it is critical to balance proline levels and proline metabolic enzyme activities to achieve proline homeostasis for proper cellular functions.

Proline metabolism may also play a role in the regulation of cellular senescence through ROS and oxidative damage (Campisi, 2013). Inhibition of PRODH expression and/or activity by genetic or pharmacological approaches has been reported to suppress DNA damage-induced senescent phenotypes (Nagano et al., 2017). In contrast, ectopic expression of wild-type PRODH induces senescence, followed by an increase in ROS and an accumulation of DNA damage (Nagano et al., 2017). On the other hand, the proline synthesis enzyme PYCR1 plays an opposite role in cellular senescence. Knockout of pycr1 in zebrafish resulted in a significant elevation of apoptosis and senescence. Adult pycr1 knockout fish also exhibited extracellular matrix contents, lowered energy, and diminished superoxide dismutase and telomerase activity when compared to wild-type fish, suggesting that pycr1 knockout fish may have mitochondrial dysfunctions (Liang et al., 2019). In general, overexpression of PRODH and depletion of PYCR1 lead to increased senescence.

Accelerated senescence has been detected in patients with schizophrenia, AD and PD (Martinez-Cue and Rueda, 2020; Solana et al., 2018). It is plausible that proline metabolism-associated senescence may play a role in schizophrenia, AD and PD. Unlike apoptosis, cellular senescence is typically defined as a state of irreversible cell cycle arrest that releases signaling factors, including proinflammatory cytokines, chemokines, and extracellular matrix proteases, termed the senescence-associated secretory phenotype (SASP) (Fielder et al., 2017). The SASP can be detected by the immune system to restore and maintain organismal health. Both ROS signaling and cellular senescence can lead to cellular immunity. The transcription factor c-Myc triggers the expression of the proline synthesis enzymes PYCR1 and ALDH18A1 in activated T lymphocytes. Additional lines of evidence suggest that proline metabolism contributes to the reprogramming of tumor-infiltrating macrophages (Abuawad et al., 2020; Kuo et al., 2020; Wang et al., 2011). Lon, a mitochondrial chaperone that interacts with PYCR1 in cancer cells, increases intracellular ROS production and activates a p38-NF-κB signaling axis, which in turn stimulates cancer cells to secrete cytokines, including TGF-β, IL-13, IL-6, and VEGF-A, to trigger M2 macrophage polarization (Kuo et al., 2020). Prodh was identified as part of innate immunity by governing ROS homeostasis, and SKN-1 is a critical transcription factor regulating the xenobiotic stress response and pathogen defense activation (Tang and Pang, 2016). In summary, many enzymes in proline metabolism involved in critical signaling pathways, including ROS, cellular senescence, and cellular immunity, suggesting that proline metabolism may play critical roles in the crosstalk of these cellular processes (Fig. 1).

**DISCUSSION**

Prolonged disturbances in cell metabolism are likely to lead to neuronal dysfunction, which in turn triggers a series of neurological and psychiatric diseases. PRODH polymorphisms are significantly associated with schizophrenia susceptibility (Guo et al., 2018). There is also evidence that defects in PRODH lead to glutamatergic and GABAergic neuron dysfunctions (Crabtree et al., 2016). However, much remains to be understood. In cancers, it has been proposed that PRODH functions as a tumor suppressor, while PYCRs function as oncogenes. Potential mechanisms include the generation of ROS, triggering cellular senescence and activating the immune system. As ROS signaling, cellular senescence and immunity may also impact the functions of neurons, it is possible that proline metabolism would affect neuronal function through mechanisms such as ROS, cellular senescence and/or cellular immunity. In summary, proline metabolism dysfunction may be a
causal link to neurological or psychiatric diseases by affecting neuronal morphology and function.

In this review, we use proline as an example to demonstrate that amino acid metabolism may play important roles in maintaining normal neuronal functions (Fig. 1). Other metabolic pathways, such as those involved in the metabolism of carbohydrates and lipids, are likely to be equally important. With the rapid development and maturation of analytical tools and cellular preparations, such as single-cell spatial multomics and human cell-derived organoids, it is hopeful that in-depth understanding of genetic, metabolic and proteomic aspects of cells and the cellular environment will yield exciting insights to shed light on therapeutic strategies for neurological and psychiatric disorders.

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AUTHOR CONTRIBUTIONS
Y.Y. and W.H. conceived and designed the study. Y.Y. performed the literature search and reviewed the previous publications on specific topics. Y.Y. and W.H. wrote the initial draft and reviewed, edited and approved the final version of the submission.

CONFLICT OF INTEREST
The authors have no potential conflicts of interest to disclose.

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