“Nutrient-Repositioning”—Unexpected Amino Acid Functions—

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Summary Repositioning is usually used to indicate drug repositioning, or the finding of new disease applications for existing, approved drugs. Nutrients can be ingested for nutritional as well as therapeutic purposes, acting much the same as drugs. Amino acids are organic compounds that possess both amino and carboxy group functionalities and are best known as building blocks of proteins in living organisms. Recent studies of individual amino acids have revealed them to be functional ingredients of new therapeutics, promoting health in addition to nutrition. Here, we propose “nutrient-repositioning”, the discovery of effects different from the existing effects of nutrients. This review summarizes some recent discoveries of unexpected amino acid functions, especially in BCAAs, histidine and serine.

Key Words repositioning, amino acid, BCAAs, histidine, serine

Nutrients such as proteins, fats and carbohydrates are substances that organisms need to live and grow. Proteins are made of amino acids which are organic compounds with amino and carboxy groups. Amino acids are also degraded for gluconeogenesis as well as biogenesis of nucleic acids, phospholipids, aminosugars, hormones and neurotransmitters. Moreover, they themselves have physiological functions through their binding proteins such as leucine and arginine, activators for the mammalian target of rapamycin complex 1 (mTORC1), a highly conserved serine/threonine protein kinase, promoting protein synthesis (translation) and inhibiting protein degradation by suppressing autophagy (1). So far, the individual amino acids have been revealed to have new physiological functions and indicated the possibilities of applying them as functional food factors (also called nutraceuticals) for promoting human health in addition to traditional nutrients.

In the pharmaceutical field, finding new efficacies of existing drugs and repurposing them for other diseases is called as drug repositioning (also known as redirecting, repurposing and reprofiling) which helps reduce the cost and risk for developing new drugs in pharmaceutical companies (2). As above, nutrients including amino acids have multiple functions and act as pharmaceuticals, so that we propose the discovery of effects different from the existing effects of nutrients as “nutrient-repositioning”. In this review, we summarize the unexpected amino acid functions found recently in branched-chain amino acids (BCAAs), histidine and serine.

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BCAAs
Leucine, valine, and isoleucine are essential amino acids called branched chain amino acids (BCAAs) and have physiological effects on protein and glucose metabolism (3). In BCAA catabolism, the first two enzymatic steps by BCAT and BCKDH are common and BCKDH is inactivated by phosphorylation by BCKDH kinase (BDK) (3). The elevated plasma BCAA levels in obesity and insulin resistance have been associated with lowered BCAA catabolism such as decreased BCAT and increased BDK expression (4). Disordered BCAA catabolism also has been reported to promote heart failure and attenuate thermogenesis (5, 6). BDK inhibitor 3,6-dichloro-benzo[b]thiophene-2-carboxylic acid (BT2) has been shown to significantly improve insulin resistance (7).

Dysregulation of glucagon is associated with the pathophysiology of type 2 diabetes. In fact, glucagon receptor antagonists have been shown to decrease blood glucose levels in type 2 diabetes. Postprandial hyperglucagonemia has been reported more pronounced than fasting hyperglucagonemia in type 2 diabetes patients. However, which nutrient stimulates glucagon secretion in the diabetic state and the underlying mechanism after nutrient intake was unclear. Recently, this has been answered by measuring plasma glucagon levels in diabetic mice after oral administration of various nutrients. Plasma glucagon levels in diabetic mice were found to be increased by ingestion of protein, especially BCAAs, but not carbohydrate or lipid (8). How do BCAAs stimulate glucagon secretion? The molecular mechanism was clarified by BDK inhibitor BT2, which suppresses the secretion in diabetic islets, suggesting that in pancreatic islet cells of the diabetic state, the
postprandial hypersecretion of glucagon is attributable to the blocking of BCAA catabolism by BDK. The suppressed BCAA catabolism has been reported in the heart, liver, and brown adipose tissue in metabolic diseases, so that it may be a common cause of various metabolic diseases, not limited to type 2 diabetes. This study not only clarifies important pathophysiological aspects of diabetes but also provides potential applications for dietary therapy.

**Histidine**

Histidine is an essential amino acid that has several functions beyond protein synthesis: a precursor for carnosine, histamine, and anti-inflammatory and immune-modulatory molecules, as well as trans-urocanate—a natural sunscreen molecule. Histidine concentrations in blood have been shown to decline in obese animals and patients (9, 10) as well as in other pathologic conditions such as chronic obstructive pulmonary disease (COPD) and kidney disease (CKD) (11, 12), while histidine concentrations and supplementation are associated with several health benefits that include but are not limited to anti-inflammatory (10, 13), antioxidant (10, 13, 14), glucoregulatory (9, 15), body weight management (9, 14), cognitive function (16), and dermatological (17).

Excess histidine is degraded through its degradation pathway requiring the coenzyme folate (tetrahydrofolate, THF) that is also essential for many metabolic pathways including nucleotide synthesis. In rapidly proliferating cells such as cancer and activated immune cells, the folate-requiring metabolic process is activated for building cells, so that folate is a target for anti-cancer and autoimmune disease therapy. A recent study has shown that histidine supplementation, to boost its degradation and consume folate, resulted in increasing the sensitivity of cancer cells to methotrexate (MTX), an anti-folate drug (18). The histidine administration with MTX dramatically suppressed tumor progression and improved survival of leukemia-bearing mice. This surprising discovery of cancer therapy by histidine supplementation can allow lower doses of the anti-folate drugs that are notorious for their side effects, especially in the brain. For clinical applications, the feasibility of histidine supplementation was addressed for enhanced anti-folate treatment in the primary and secondary sites of pediatric acute lymphoblastic leukemia (ALL)—the blood and the brain, in ALL mouse models. Further, in humans, excess histidine was detected in the plasma following histidine supplementation, but currently no such data exist for the brain, and for the site of leukemia brain lesions—the cerebrospinal fluid (CSF). Therefore, the levels of histidine were studied with disease progression and following anti-folate therapy in the brains of pediatric ALL patients with and without central nervous system (CNS)-involvement in the leukemia. These studies will guide further investigation in ALL mouse models, where feasibility and optimal timing and duration of histidine supplementation for enhanced anti-cancer therapy can be identified. Further, this work will inform clinical studies in patients treated with anti-folate therapy. The potential to develop modern treatments that incorporate metabolic drugs or dietary therapy enhancement is transformative for health equity; proposing to incorporate a cost-effective therapy or nutritional modifications, which can be financially accessible to all, in the standard-of-care regime and offer more hope to patients from underserved communities.

**Serine**

Serine is a non-essential amino acid that is important for maintaining normal functions of the nervous system. It is a precursor for the synthesis of phosphoglycerols and complex macromolecules such as sphingolipids and glycolipids, which are important membrane components and myelin constituents (19). When neuronal cells are cultured under serine-deficient conditions, the concentrations of phosphatidylserine and sphingolipids decrease. Demyelination contributes to the development of neuropathic pain by disrupting the molecular and structural features of nerve fibers (20). Patients with hereditary serine deficiency are reported to have polyneuropathy (21). Additionally, there is a report that the serine concentration in blood decreases with age (22). These findings indicate the importance of serine for maintaining normal function of the nervous system. The localized inflammation of the dorsal root ganglion (DRG) has also been proposed to play an important role in neuropathic pain. Inflammatory processes within the DRG per se change excitability of the DRG neurons (23). Early work has demonstrated the importance of the ω-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid, in attenuating inflammation in the DRG (24). The serine biosynthesis system in the DRG is affected in a nonclinical model of painful peripheral neuropathy (25). Based on the above findings, it was hypothesized that the combination of serine, which provides necessary components for maintaining nerve function, and EPA, which exerts anti-inflammatory properties, could synergistically alleviate chronic pain, especially in the DRG.

Multisite pain, including low-back and knee pain, is a major health issue that greatly decreases quality of life. The effects of serine and EPA ingestion were demonstrated in a study on pain scores of adults with pain in the low back and/or knee for at least 3 mo (26). The participants (n=120) were randomly allocated to either the active group (daily ingestion of 594 mg serine and 149 mg EPA) or placebo group, and the study was conducted in a double-blind manner. The Japan Low Back Pain Evaluation Questionnaire (JLEQ) scores at week 8 were lower in the active group. The Japanese Knee Osteoarthritis Measure (JKOM) scores at week 4, week 8, and week 12 were also lower in the active group. Additionally, the active group had 11–27% better scores compared with the placebo group for the Brief Pain Inventory. No adverse events were observed. Serine and EPA were effective for pain relief in adults with low-back and knee pain.
Disclosure of state of COI
No conflicts of interest to be declared.

REFERENCES


