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REVIEW ARTICLE

Alterations of amino acid metabolism in osteoarthritis: its implications for nutrition and health

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Abstract Osteoarthritis (OA) is a common form of arthritis in humans. It has long been regarded as a non-inflammatory disease, but a degree of inflammation is now recognized as being a vital inducer of subpopulation of OA. Besides inflammation, the establishment and development of OA are associated with alterations in metabolism and profiles of amino acids (AA), including glutamate- and arginine-family AA as well as their related metabolites (e.g., creatinine, hydroxyproline, γ-aminobutyrate, dimethylarginines and homoarginine). Functional AA (e.g., glutamine, arginine, glutamate, glycine, proline, and tryptophan) have various benefits (i.e., anti-inflammation and anti-oxidation) in treatment of inflammation-associated diseases, including OA. Thus, these AA have potential as immunomodulatory nutrients for patients with inflammation-induced OA.

Keywords Arginine · Glutamate · Glutamine · Inflammation · Osteoarthritis

Abbreviations
AA   Amino acid(s)
HSP   Heat shock proteins
IκB   Inhibitor of κBs

IL   Interleukin
iNOS   Inducible nitric oxide synthase
MMP   Matrix metalloproteinase
NF-κB   Nuclear factor-κB
NO   Nitric oxide
OA   Osteoarthritis
PPAR γ   Peroxisome proliferator-activated receptor-γ
SAM   S-Adenosylmethionine
TNF-α   Tumor necrosis factor-α

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Introduction

Osteoarthritis (OA) is a common form of arthritis characterized by articular cartilage destruction and osteophyte formation (Berenbaum 2013). It is a painful and disabling disease and reduces life quality of patients. The exact etiology of OA is still unknown, but various risk factors have been reported, including age (Blagojevic et al. 2010), obesity (Koonce and Bravman 2013), metabolic syndrome (Karlson et al. 2003), genetic predisposition (Spector et al. 1996), malalignment (Felson et al. 2013), acute joint injury (Gelber et al. 2000), and reduced sex hormone levels (Arden and Nevitt 2006). At present, there is no drug approved for structural protection of the joint or prolongation of joint life. With the growing understanding about OA, it can be divided into at least four subpopulations: (a) synovium-driven, (b) cartilage-driven, (c) bone-driven, and (d) other idiopathic conditions that remain to be understood (Siebuhr et al. 2015). OA has long been regarded as a non-inflammatory disease, but a degree of inflammation is now recognized as being a vital part of OA pathology (Siebuhr et al. 2015; Goldring and Otero 2011). Elevated levels of inflammatory mediators, such as interleukin (IL)-1β, IL-6, and IL-8, have been detected in both the synovial fluid and

the serum from people with OA (Attur et al. 2013; Siebuhr et al. 2015). The inflammation and inflammation-related molecules from other underlying pathologies, such as trauma, metabolic syndrome and age, contribute to the initiation and persistence of OA, and synergize with other risk factors in the pathogenesis of OA (Sellam and Berenbaum 2010; Berenbaum 2013). For example, nuclear factor-κB (NF-κB) pathway is activated in OA disease by proinflammatory cytokines (i.e., tumor necrosis factor-α and IL-1β; Marcu et al. 2010). Once activated, the NF-κB signaling induces expression of various catabolic genes in articular chondrocytes (Marcu et al. 2010), including a disintegrin and matrix metalloproteinase (MMP) with thrombospondin motifs (ADAMTS)-5, inducible nitric oxide (NO) synthase (iNOS) and matrix metalloproteinase-13, which are highly involved in the pathogenesis of OA (Gao et al. 2015; Yang et al. 2014; Xu et al. 2013). Subsequently, inflammation has been regarded as a driver of joint destruction, OA symptoms, and progression of OA in a subpopulation of OA patients (Siebuhr et al. 2015).

Alterations of amino acid profiles in OA

Amino acids (AA) are not only building blocks of peptides and proteins, but are also precursors of low molecular weight substances (e.g., NO, dopamine, serotonin, polyamines, glucosamine, creatine, glutathione, homoarginine, and agmatine) with enormous physiological functions (Hou et al. 2015a; Yang et al. 2015a; Tsikas and Wu 2015; Wu 2013a, 2013b). For example, physiological concentrations of arginine (Jobgen et al. 2009a, b; Wu et al. 2013), glycine (Wang et al. 2013, 2014a, b), glutamine (Haynes et al. 2009; Wang et al. 2015b; Yi et al. 2015; Zhu et al. 2015), glutamate (Jiao et al. 2015; Rezaei et al. 2013a, b), proline (Obayashi et al. 2012, 2015; Wu et al. 2011a), cysteine (Hou et al. 2015b; Wu et al. 2004), and tryptophan (Yao et al. 2011) inhibit oxidative injury in cells. Furthermore, as an inhibitor of iNOS expression, glucosamine (a metabolite of glutamine) has been proposed to alleviate inflammation in OA patients (Meininger et al. 2000). This is analogous to the use of anti-inflammatory proteins (e.g., interferon-tau) to inhibit inflammation-induced cell injury under physiological (e.g., pregnancy) and pathological (e.g., autoimmune disease) conditions (Bazer et al. 2015).

Besides inflammation, alterations in AA metabolism and profiles are also involved in the pathogenesis of OA (Dimitroulas et al. 2015; Mayboroda et al. 2007; Mickiewicz et al. 2015; Wen et al. 2015). In a recent study, Zignego et al. (2015) employed liquid chromatography-mass spectrometry-based metabolomics to understand short-term metabolic responses of human chondrocytes to sub-injurious physiological compression. Based on changes

in the concentrations of threonine, homoserine, and allo-threonine, these authors suggested that rates of glycine, serine, and threonine metabolism were increased after mechanical loading (Zignego et al. 2015). Results of the analysis of metabolites in synovial fluid by magnetic resonance spectroscopy-based metabolomics indicated that an anterior cruciate ligament reconstruction injury resulted in perturbed pathways for the metabolism of: (a) glycine, serine and threonine; (b) arginine and proline; and (c) alanine, aspartate, and glutamate in patients (Mickiewicz et al. 2015). As such, the profiles of glycine, serine, creatine, choline, hydroxyproline, proline, asparagine, succinate, alanine, and histidine were altered in subjects with injured joints (Mickiewicz et al. 2015). In rabbits with an anterior cruciate ligament reconstruction injury, there are marked changes in plasma levels of AA, particularly alanine, threonine and methionine (Ohnishi et al. 2013). Likewise, there are negative correlations between histological assessments and changes in plasma concentrations of many AA (including arginine, glutamate, citrulline, ornithine and hydroxyproline; Ohnishi et al. 2013). Furthermore, sheep with anterior cruciate ligament transaction exhibited decreases in serum concentrations of tyrosine, valine, isoleucine, and leucine, but increases in serum concentrations of glycine and 3-methylhistidine at week 4 after surgery, compared with the sham control (Maher et al. 2012). The animals also had lower concentrations of serum valine, isoleucine, and leucine, but higher concentrations of serum glutamine, creatine, creatinine and 3-methylhistidine at week 12 after surgery, than those from the sham surgery (Maher et al. 2012). Indeed, the ratio of branched-chain AA to histidine, including the ratios of valine to histidine and leucine or isoleucine to histidine, is potentially a useful biomarker for osteoarthritis (Zhai et al. 2010). With the use of ultra-performance liquid chromatography coupled to mass spectrometry, fourteen significantly altered metabolites were eventually identified in the serum of OA, compared to healthy controls (Zhang et al. 2015). Among them, serum levels of 4-oxoproline, glycine and histidine were decreased, while serum levels of tryptophan were increased in OA, compared to healthy controls (Zhang et al. 2015). The amount of plasma iNOS in the OA group was higher than that in healthy controls (Suantawee et al. 2015). This result indicates changes in arginine metabolism in OA patients, as arginine is the physiological nitrogenous substrate for iNOS (Wu et al. 2009). In support of this view, OA patients have a lower concentration of arginine, a lower ratio of arginine/asymmetric dimethylarginine, and a higher concentration of symmetric dimethylarginine in the plasma, compared to healthy controls (Pascale et al. 2013). Also, concentrations of arginine and asymmetric dimethylarginine in synovial fluid are higher than that in the plasma of OA patients (Pascale et al. 2013). Similarly, altered concentrations

of arginine, homoarginine and dimethylarginines in the plasma of OA patients have recently been reported by other researchers (Kayacelebi et al. 2015).

Anti-inflammatory treatments in OA

Anti-inflammatory treatments by targeting inflammatory cytokines, such as IL-1β, IL-23 and TNF-α, are used in inflammation-related diseases such as rheumatoid arthritis, gout, juvenile idiopathic arthritis, and ankylosing spondylitis (Tyring et al. 2006; Whibley and Gaffen 2015; Ren et al. 2013f, 2015; Wang et al. 2015a). The benefits of anti-inflammatory treatment are also observed in OA. Oral administration of naringin attenuates TNF-α-mediated inflammation and catabolism in chondrocytes, alleviates degradation of cartilage matrix, and protects against OA development in surgically induced mouse OA models through inhibition of NF-κB pathways (Zhao et al. 2015). Berberine reduces the induction of IL-1β expression in response to connective tissue growth factor and reverses cartilage damage in an experimental rat model of collagenase-induced OA (Liu et al. 2015). Through its anti-inflammatory property, diosgenin inhibits production of NO and prostaglandin E2, and expression of MMP-3, MMP-13, iNOS, and cyclooxygenase-2 in human OA chondrocytes (Wang et al. 2015a, b). Interestingly, one study has explored an anti-TNF-α therapy in OA by conducting an open-label evaluation of adalimumab over 12 weeks in 20 patients with OA of the knee (Maksymowych et al. 2012). After anti-TNF-α therapy, the authors observed a significant improvement in mean WOMAC pain, stiffness, function, physician and patient global, as well as target joint swelling at 12 weeks (Maksymowych et al. 2012). This result indicates that targeting TNF-α may be of therapeutic benefit in OA. However, anti-inflammatory treatments in OA by other investigations have shown limited effects (Siebuhr et al. 2015; Chevalier et al. 2009; Cohen et al. 2011), possibly due to the lack of preselection of patients with inflammation, ineffective drugs, and suboptimal treatment procedures. Nonetheless, these interesting studies show that anti-inflammatory treatments may be a potentially effective therapy for OA, especially for patients with inflammation-induced OA. Thus, the development of drugs with active anti-inflammatory properties is promising in treating this inflammatory disease.

AA interventions in OA

Nutritional interventions and nutraceutical applications for medical conditions are currently riding the crest of public enthusiasm. Based on the alterations in AA metabolism and AA profile in the pathogenesis of OA, it is potentially attractive to use nutritional interventions with AA to manipulate the pathogenesis of OA. Indeed, nutritional interventions with functional AA are beneficial in various models, such as mice with virus or bacteria infection (Ren et al. 2012b, 2013d), mice with vaccine immunization (Ren et al. 2013g), and mice with inflammatory disease (Ren et al. 2014b). The following sections highlight glutamine, arginine, glutamate, aspartate, and *S*-adenosylmethionine.

Glutamine

Glutamine is the most prevalent AA in both body fluids and skeletal muscle and is considered as a nutritionally essential AA under specific physiological conditions, such as malnutrition, infection and inflammation (Ren et al. 2012a, 2013c, 2013d, 2013e; Wu et al. 2011b). Glutamine has an anti-inflammatory role in various intestinal inflammatory models through its regulatory function in signaling pathways, including NF-κB, signal transducer and activator of transcription (STAT), mitogen-activated protein kinases, phosphoinositide 3-kinase-protein kinase B, activating protein-1, NOS-NO, peroxisome proliferator-activated receptor-γ (PPAR γ), heat shock factor-1-heat shock proteins (HSP), and glutathione-reactive oxygen species (Ren et al. 2013f). For example, glutamine inhibits NF-κB signaling through three levels. At the NF-κB level, glutamine inhibits NF-κB protein expression and the dimer (p50 and p65) translocation from the cytoplasm to the nucleus and promotes p65 protein degradation through the phosphorylation at serine-536. At the inhibitor of κBs (IκB) level, glutamine reduces its ubiquitination and degradation through the decrease of IκB phosphorylation. At the IκB kinase level, glutamine decreases IκB kinase-α and IκB kinase-β abundance (Ren et al. 2013f). Thus, glutamine has anti-oxidative functions not only in inflammatory diseases of the intestine, but also in other inflammation-associated diseases, such as arthritis and asthma (Ren et al. 2013f). Indeed, in the dextran sulfate sodium-induced colitis model, which is similar to human ulcerative colitis, dietary glutamine supplementation has beneficial effects on clinical and biochemical parameters (i.e., total superoxide dismutase, IL-17 and TNF-α) in colitis model, and these results are associated with colonic NF-κB and phosphoinositide 3-kinase-protein kinase B signaling pathways, suggesting glutamine could be a potential therapy for intestinal inflammatory diseases (Ren et al. 2014b). Glutamine could be also as an adjuvant therapy for OA with its anti-inflammatory function. Notably, glutamine treatment affects expression of HSP70 in articular chondrocytes, abrogates the cytotoxic outcome of sodium nitroprusside dehydrate in chondrocytes, and renders chondrocytes unsusceptible

to NO-induced apoptosis (Tonomura et al. 2006). Furthermore, glutamine treatment affects expression of aggrecan and HSP70, and the severity of OA in rat models (Fujita et al. 2012). However, these observed benefits of glutamine in chondrocytes and in animal OA models depend on HSP70 (Fujita et al. 2012; Tonomura et al. 2006). Thus, whether glutamine exerts beneficial roles on OA patients through anti-inflammation merits further investigations.

Arginine

Arginine had long been considered as a nutritionally non-essential AA for adult animals and humans, but has recently been classified as a nutritionally semi-essential AA for young mammals (such as rats, swine, and infants), as well as males and females in certain situations (Wu 2014; Wu et al. 2014a). This is because the rate of arginine utilization in the whole body is greater than the rate of arginine synthesis under certain conditions (e.g., early weaning, lactation, pregnancy, inflammation, burns, injury, infection, heat stress, and cold stress) (Wu et al. 2014a; Wu 2009; Ren et al. 2012b). In humans, pigs, and rats, most of dietary arginine is metabolized via arginase and arginine–glycine amidinotransferase pathways, but the production of NO from arginine by NO synthase plays an important role in immune responses (Wu et al. 2009). It is now known that three isoforms of NOS generate NO from arginine in a cell-specific manner (Wu et al. 2009). The nutritional significance of this metabolic pathway is supported by the observations that dietary supplementation with arginine improves immunity, leading to the killing of pathogens (e.g., bacteria and virus) (Ren et al. 2012b, 2013g, 2014a, 2014b; Li et al. 2007). At molecular and cellular levels, arginine activates both cell- and antibody-mediated immune responses in mice (Ren et al. 2013g, 2014a; Shang et al. 2003), humans (Moriguti et al. 2005), chickens (Munir et al. 2009; Perez-Carbajal et al. 2010), pigs (Chen et al. 2012), and fish (Pohlenz et al. 2012). Interestingly, arginine has various benefits in mice with dextran sulfate sodium-induced colitis, including improvements in clinical parameters of survival, body weight loss, colon weight, and reduction of colonic permeability, number of myeloperoxidase-positive neutrophils, and expression of proinflammatory cytokines and chemokines (Coburn et al. 2012). Indeed, in our previous study, we also found arginine supplementation increased colon length, superoxide dismutase activity, and claudin-1 expression, while alleviating infiltration of neutrophils, expression of IL-17 and TNF-α, and activation of colonic phosphoinositide 3-kinase-protein kinase B and myosin light-chain kinase-myosin light chain-20 pathways (Ren et al. 2014b). These findings suggest that it is fruitful to suppress the pathogenesis of OA by manipulating arginine metabolism. S-Methylisothiourea, an iNOS inhibitor, reduces the release of MMP-13, TNF-α, prostaglandin E2, and nitrite in stimulated rabbit cartilage media, while attenuating the production of nitrite, prostaglandin E2, IL-1β and TNF-α from synovial explants. (Balaganur et al. 2014). These results indicate chondroprotective and anti-inflammatory effects of S-methylisothiourea in OA. N-iminoethyl-L-lysine, an iNOS inhibitor, has a beneficial effect in OA through: (a) preventing lipid peroxidation and reactive oxygen species production via NO-dependent and/or independent mechanisms; (b) attenuating 4-hydroxynonenal (a product of LPO)-induced cell death; and (c) different mediators of cartilage damage (Bentz et al. 2012).

Glutamate and aspartate

Glutamate and aspartate are excitatory AA neurotransmitters in the mammalian central nervous system. Glutamate and aspartate are associated with the production of ATP and other biological active molecules, including glutamine, glutathione, proline, ornithine, and arginine, thereby affecting cell metabolism and signaling, host anti-oxidative ability, immunity under physiological and pathological conditions, and animal growth performance (Rezaei et al. 2013a, 2013b; Wu 2009, 2010). Dietary supplementation with glutamate or aspartate protects hosts from damage caused by stimulators exposure, such as decrease in oxidative stress, alteration of serum AA concentrations, and changes in expression of intestinal AA transporters (Duan et al. 2014, 2015; Wu et al. 2014b, 2014c). Glutamate or aspartate may have vital role in the acute and ongoing progressive processes of soft tissue injuries that impact early OA development because there is a significant increase in levels of glutamate and aspartate in the microdialysates of anterior cruciate ligament transected knee joints in rats, compared to those in the contralateral sham-operated knee (Jean et al. 2005). Additionally, glutamate and aspartate in synovial fluid from patients with synovitis are 54 and 28 times higher, respectively, than those from healthy controls, suggesting that glutamate and aspartate may contribute to the pathogenesis of human arthritic conditions (McNearney et al. 2000). Additionally, γ-aminobutyrate (a product of glutamate decarboxylation) may affect OA progress possibly by blocking the activation-induced calcium signal and inhibiting NF-κB activation (Huang et al. 2015). Further studies have demonstrated the significant associations between glutamate or aspartate and inflammatory mediators, such as TNF-α, regulated on activation normal T cell expressed and secreted (RANTES) protein, and IL-8, in the synovial fluid of patients with active inflammatory arthropathies, such as rheumatoid arthritis, acute gout, and symptomatic OA (McNearney et al. 2004; 2010). Indeed,

bone and joints have the components of glutamate signaling, including glutamate receptors, glutamate transporters, and vesicular glutamate transporters (Wen et al. 2015). Thus, glutamate or aspartate can be used as therapeutic targets for OA. Intrathecal administration of ketamine, an uncompetitive N-methyl-d-aspartate receptor channel blocker, reduces the pain and severity of arthritis in antigen-induced arthritis in rats, including reductions in joint swelling and infiltration of inflammatory cells into the joint cavity (Boettger et al. 2010). A Phase II trial of LY545694, an antagonist of ionotropic glutamate receptor 5, in the treatment of knee OA pain has been completed (Martel-Pelletier et al. 2012; Wen et al. 2015), and some benefits have been observed.

Other functional amino acids and metabolites

S-adenosylmethionine (SAM) is the activated form of methionine and is a methyl group donor in protein and DNA methylation reactions (Wu 2013a, b). SAM has been reported to protect synovial cells through promoting glutathione peroxidase production, and blocking the activity and synthesis of enzymes that degrade cartilage (Lieber and Packer 2002; Lopez 2012). SAM may also protect cartilage proteins and proteoglycans in the joint lining. These results suggest an interesting therapeutic potency of SAM in the pathogenesis of OA. Indeed, SAM is effective to treat OA, and the efficacy is equal to, even more effective, and better tolerated than administration of indomethacin or ibuprofen (Glorioso et al. 1985; Vetter 1987). Moreover, the clinical improvements achieved by the 12-week treatment with SAM on 45 patients with knee OA can sustain for a longer period of time than with piroxicam treatment (Maccagno et al. 1987).

In a study to investigate the efficacy of creatine (a product of arginine, glycine and methionine metabolism) supplementation combined with strengthening exercises in OA, the authors found that creatine supplementation can improve physical function, stiffness subscales, lower limb lean mass, and quality of life, while reducing the pain for OA patients (Neves et al. 2011). Thus, creatine administration has potential to be used as adjuvant therapy for OA.

Conclusion and perspectives

The establishment and development of OA are associated with inflammation and alterations in AA metabolism and profiles. Emerging evidence shows that OA patients have lower concentrations of plasma L-valine, L-isoleucine, and L-leucine (Maher et al. 2012; Zhai et al. 2010), but higher concentrations of plasma L-glutamate and L-aspartate (McNearney et al. 2000; Jean et al. 2005), compared to healthy controls. As most AA have numerous biological functions in vivo (Wu 2009, 2010; Chen et al. 2014), they may be considered in nutritional therapy of OA through dietary supplementation. Additionally, results of recent research indicate that some functional AA can have benefits on inhibiting the pathogenesis of OA and alleviating its complications. It is interesting to uncover the regulatory functions of other AA in the initiation, establishment, development and progression of OA, such as proline, threonine, glycine, tryptophan, and methionine. For example, proline has been demonstrated to regulate immune responses in virus or bacteria infected models (Ren et al. 2013a, 2013b). Threonine and methionine are reported to regulate epithelial cell migration and proliferation, cell differentiation, restoration of epithelial barrier functions, and modulation of cell apoptosis, thereby enhancing mucosal healing after intestinal mucosal inflammation (Lan et al. 2015) and modulating autophagic responses of porcine intestinal epithelial cells to enterotoxigenic *Escherichia coli* infection (Tang et al. 2015). Furthermore, leucine, which can inhibit NO synthesis (Yang et al. 2015b), may also be effective to attenuate the progression of OA. Further research is necessary to provide much-needed data on roles of functional AA in the prevention and treatment of OA.

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