Jurnal Sains Kesihatan Malaysia **7** (1) 2009: 1-11

Kertas Ulasan/*Review Article*

Amino Acids and Muscle Protein Metabolism with Aging

(Metabolisme Asid Amino dan Protein Berkaitan dengan Penuaan)

SATOSHI FUJITA

ABSTRACT

Sarcopenia is age-associated loss of skeletal muscle mass and strength which develops slowly over decades and becomes a significant factor to disability among the elderly population. Although several mechanisms of sarcopenia have been proposed, they all seem to affect the balance between muscle protein synthesis and breakdown, resulting in the net muscle loss. In present article, the most recent findings regarding the role of nutritional intake on muscle protein metabolism in the elderly will be reviewed. Particular focus will be given to dietary protein requirement for elderly, acute anabolic response of amino acids and protein intake, age-associated changes in the response of muscle protein to a meal intake, and the role of insulin resistance of muscle protein metabolism among the elderly. Finally, possible benefits and risks of protein and amino acid supplements for the prevention and treatment of sarcopenia will also be reviewed.

Key words: Sarcopenia, Amino Acid Metabolisme, Muscle Metabolism, Older People

ABSTRAK

Sarkopenia adalah kehilangan jisim dan kekuatan otot rangka yang berkaitan dengan penuaan yang terhasil secara perlahan dan merupakan faktor utama disability di kalangan populasi warga tua. Walaupun beberapa mekanisme sarkopenia telah dikemukakan, semuanya adalah berkaitan dengan keseimbangan sintesis dan penguraian protein yang akhirnya mengakibatkan kehilangan jisim otot. Di dalam artikel ini, penemuan mutakhir berkaitan dengan peranan diet ke atas metabolism protein di kalangan warga tua akan diulas. Fokus perbincangan adalah keperluan protein warga tua, tindak balas anabolik akut asid amino dan pengambilan protein, perubahan berkaitan dengan penuaan dalam tindak balas protein otot dengan pemberian makanan, *dan peranan kerintangan insulin terhadap metabolism protein di kalangan warga tua. Akhirnya, kebaikan dan risiko suplemen protein dan asid amino bagi pencegahan dan rawatan sarkopenia juga akan diulas.*

Kata kunci: Sarkopenia, Metabolism Asid Amino, Metabolism Otot, Warga tua

INTRODUCTION

Aging is associated with a progressive reduction of skeletal muscle mass (Lexell 1995) and concomitant reduction in strength (Frontera et al. 1991). This age-related involuntary muscle loss is called sarcopenia (from Greek *sarx* for flesh and *penia* for loss). After 30 years of age, about 3 to 5% of muscle mass is lost per decade, and this reduction accelerates even further after 60 years (Holloszy 2000; Melton et al. 2000). Sarcopenia increases the risk of injury due to falls which may take away the physical independence and lead to disability (Wolfson et al. 1995; Tinetti & Williams 1997). Loss of skeletal muscle also reduces physical activity level which may lead to metabolic complications, including osteoporosis, obesity and glucose intolerance (Dutta and Hadley 1995; Evans 1995). Skeletal muscle is also an important source of amino acids which provide substrates for wound healing during malnutrition, starvation, injury and disease (Reeds et al. 1994). Clear mechanisms which trigger sarcopenia have not been clarified, but they are likely to be multifactorial, and they all appear to affect the balance between muscle protein synthesis and breakdown rate, which subsequently results in the loss of muscle mass (Dutta and Hadley 1995).

In this review, discussion will be focused on the age associated changes in muscle protein metabolism in relation to nutrient intake, which has an important implication in the pathogenesis of sarcopenia.

BASAL MUSCLE PROTEIN METABOLISM

For healthy adults, muscle mass is maintained with exquisite balance of muscle protein synthesis (eg. nutritional intake, muscle contraction, etc.) and muscle breakdown (eg. fasting, stress, etc.) which occur continuously throughout the day. Several studies have consistently reported that the rate of muscle protein breakdown does not change by aging (Yarasheski et al. 1993; Welle et al. 1995; Hasten et al. 2000; Volpi et al. 2000; Volpi et al. 2001). Consequently, investigators have focused on the muscle protein synthesis rate at postabsorptive (basal) and postprandial (fed) state. While some studies have indicated the age associated decrease in the basal muscle protein synthesis rate (Welle et al. 1993; Balagopal et al. 1997), others did not confirm such reduction in muscle protein synthesis with aging (Volpi et al. 2001; Fujita et al. 2007). Although the reason for such discrepancy is not clear, the differences in health, nutritional status, physical activity level of elderly subjects participated in the experimental protocols may have played a significant role. Furthermore, in those studies reporting the reduced muscle protein synthesis, muscle protein breakdown rate was estimated indirectly by whole body approaches (Welle et al. 1993; Balagopal et al. 1997). These methods make it difficult to determine accurately if the subjects were experiencing a reduction in net muscle protein balance (i.e. net muscle loss) since one would not lose muscle mass if the reduced muscle protein synthesis was balanced by concomitant reduction in muscle protein breakdown (i.e. reduced muscle protein turnover).

If the basal muscle protein balance, which occupies most of catabolic phase of metabolism in a day, does not change with aging, then the factors contributing to development of sarcopenia may relate to abnormality in the anabolic phase of muscle metabolism.

PROTEIN REQUIREMENT FOR THE ELDERLY POPULATION

It has been reported by Institute of Medicine in USA that the daily protein requirement for older adults is estimated to be similar to that of adults 55 years and younger (0.8g.kg^{-1}.day^{-1}) (Food et al. 2002). However, information regarding the dietary protein requirement of elderly population is still limited. Although several studies support the 0.8g.kg^{-1}.day^{-1} recommendation, others have suggested that a moderately higher protein intake of 1.0-1.3 g.kg^{-1}.day^{-1} may be required to maintain nitrogen balance and muscle mass in elderly individuals (Campbell et al. 2001). In support of this hypothesis, Campbell et al. (2001) have reported that protein intake of (0.8g.kg^{-1}.day^{-1}) for 14-week period in a metabolic ward resulted in a significant reduction in muscle cross sectional area of the thigh in the elderly subjects, even while consuming a weight maintenance diet (Campbell et al. 2001). Further studies are warranted to clarify the optimal amount of dietary protein intake for the elderly population with different health, dietary status, and physical activity level.

MUSCLE ANABOLIC RESPONSE TO AMINO ACIDS AND PROTEIN

Nutrient intake, especially protein and amino acids, is the most important anabolic stimuli for skeletal muscle (Bohe et al. 2003; Paddon-Jones et al. 2006). Amino acids ingestion and subsequent rise in blood concentration of amino acids rapidly increases inward transport of amino acids into muscle cell and subsequently increases muscle protein synthesis in a dose-dependent process (Bohe et al. 2003; Paddon-Jones et al. 2004; Carroll et al. 2005).

In order for orally ingested amino acids to reach the systemic target tissue, they first need to pass through the splanchnic tissues (eg. gut, liver, etc.).

Although amino acid extraction by the first-pass is higher in older subjects than young (Boirie et al. 1997), this does not appear to influence the systemic amino acid concentration (Volpi et al. 1999). Consequently, oral amino acid intake increases amino acid delivery to the leg and muscle protein synthesis to the same degree in the elderly and young subjects (Volpi et al. 1999).

On the contrary to fast absorbing amino acids, the speed of digestion for intact protein and amino acid absorption from the gut has a major effect on whole-body protein anabolism (Boirie et al. 1997; Dangin et al. 2001). In young subjects, proteins that are digested slowly (i.e. casein protein) appear to induce an overall better anabolic response at the whole-body level as compared with proteins that are digested more rapidly (i.e. whey protein) (Boirie et al. 1997; Dangin et al. 2001). However, in elderly individuals, it appears that proteins that are rapidly digested and absorbed induce a better anabolic response as compared with the slower proteins(Dangin et al. 2002).

ESSENTIAL AMINO ACIDS

Studies have indicated that the anabolic action of amino acids on muscle proteins is due mainly to the essential amino acids (EAAs) (Volpi et al. 2003). This has been confirmed in older subjects by administering nutritional supplements containing only EAAs or a balanced essential and nonessential amino acid mixture containing the same amount of EAAs but double the amount of amino acids and amino-nitrogen (Volpi et al. 2003). Under these conditions, muscle protein synthesis was stimulated to the same extent by either supplement in the elderly subjects (Volpi et al. 2003).

Among the essential amino acids, branched-chain amino acids (BCAAs) have been shown to be most responsible for the direct stimulation of muscle protein synthesis. Specifically, leucine is the most potent of the BCAAs for the stimulation of muscle protein synthesis. Intake of leucine alone can activate several intracellular signaling proteins involved in initiating mRNA translation, including the mammalian target of rapamycin (mTOR), 70-kDa ribosomal protein S6 kinase (S6K1), and eukaryotic initiation factor 4E binding protein-1 (4E-BP1) (Anthony et al. 2000a; Anthony et al. 2000b; Anthony et al. 2001).

Recently, age specific changes in muscle anabolic response to EAAs have been revealed. Katsanos et al. (2005) have demonstrated that older subjects had significantly less muscle protein accretion than younger subjects following the ingestion of a 7g EAAs supplement. In a more recent study, the same authors found that while both a 26% (1.7g leucine in 7g EAAs) and a 41% (2.8g leucine in 7g EAAs) leucine EAAs ingestion increased muscle protein synthesis in young men, only the 41% leucine EAAs bolus was effective in stimulating muscle protein synthesis in elderly men (Katsanos et al. 2006). Although large amount of EAAs (~15g) exert similar effects in the elderly and young persons (Volpi et al. 1999;

Paddon-Jones et al. 2004), studies above indicate that the age-related differences in the muscle anabolic response becomes apparent when submaximal amount of amino acids are given.

COMPARISON OF INTACT PROTEIN AND FREE-FORM ESSENTIAL AMINO ACIDS ON MUSCLE PROTEIN ANABOLISM IN THE ELDERLY

Paddon-Jones et al. (2006) have demonstrated that ingestion of 15g of EAAs more than doubles muscle protein balance in elderly persons when compared to that of the ingestion of 15g whey protein, which would support a greater importance of EAAs, as opposed to intact protein, in improving muscle protein accretion in older population. On the contrary, ingestion of only the EAAs part of whey protein (about 7g of EAAs) does not improve muscle protein balance as much as 15g whey protein ingestion (Katsanos et al. 2008). These results are consistent with the recent finding that leucine does not provide any additional benefit on post-exercise muscle protein anabolism when sufficient amount of protein is ingested (Koopman et al. 2008). Therefore, current evidence suggests greater nitrogen retention with intact protein versus free-form amino acids when provided as dietary supplement in the elderly population (Katsanos et al. 2008).

LONG-TERM CLINICAL STUDIES ON AMINO ACIDS AND PROTEIN SUPPLEMENTS

Although muscle anabolic effect of amino acids and protein intake among the elderly persons is evident in the acute studies (Bohe et al. 2003; Paddon-Jones et al. 2006), long-term clinical studies to increase muscle mass with either amino acids or protein have reported mixed results (Fiatarone et al. 1994; Welle et al. 1998; Solerte et al. 2008b; Verhoeven et al. 2009). Fiatarone et al. (1994) have demonstrated that while resistance training increased muscle strength of frail elderly, intake of high-protein supplement alone did not affect either muscle mass or strength. There are several possible mechanisms for these negative study results. First of all, it is difficult to increase caloric intake or protein intake by nutritional supplement in older people. When older people consume nutritional supplement, they naturally compensate by consuming fewer calories from their ad libitum diet (Fiatarone et al. 1994; Fiatarone Singh et al. 2000). Secondly, it is also possible that elderly persons have a diminished ability to respond to a mixed supplement which contains not only proteins but also other nutrients such as carbohydrate and fats. Many of studies which reported no beneficial effect of nutritional supplement used either the mixed supplement (Fiatarone et al. 1994; Welle and Thornton 1998) or co-ingested the amino acid supplement with regular meal (Verhoeven et al. 2009).

ENDOGENOUS HORMONE RESPONSE AND MUSCLE AMINO ACID UTILIZATION

Mixture of amino acids with other nutrient, specifically carbohydrate, has profound impact upon the endogenous hormone response and muscle metabolism (Volpi et al. 2000). When the carbohydrate was added to the amino acid mixture, muscle protein synthesis almost doubles in young subjects, while addition of carbohydrate did not have any additional anabolic response in older subjects (Volpi et al. 2000). In fact, addition of carbohydrate interfered with muscle protein breakdown as well as muscle protein anabolism by amino acids, leading to decreased muscle protein turnover (Volpi et al. 2000).

Insulin is a potent muscle anabolic agent. However, insulin resistance of muscle protein metabolism with aging appears to be responsible for this blunted response to mixed supplement. Recent data using various levels of physiological hyperinsulinemia have demonstrated that vasodilation and subsequent increase in nutrient flow to the muscle are important regulators of muscle anabolic response during hyperinsulinemia (Fujita et al. 2006). The existence of insulin resistance of muscle protein metabolism with aging, independent of glucose tolerance, has been recently demonstrated in healthy, non-diabetic elderly subjects (Rasmussen et al. 2006). This blunted response of muscle anabolism to insulin is associated with reduction in endothelium-dependent vasodilation and blood flow (Rasmussen et al. 2006). Interestingly, this insulin resistance of muscle protein metabolism in the elderly can be reversed by aerobic exercise through improved endothelial function, insulin-induced vasodilation, and intracellular insulin signaling (Fujita et al. 2007).

RISK OF EXCESSIVE AMINO ACIDS AND PROTEIN INTAKE

Although it is clear that insufficient intake of protein over a prolonged period of time results in an accelerated loss of muscle mass in the elderly population (Castaneda et al. 1995a; Castaneda et al. 1995b), excessive intake of protein in human is also associated with series of adverse events. Daily intakes of protein above 45% on an energy basis in adults are associated with weakness, nausea, diarrhea and ultimately death, whereas daily intakes of 20-25% protein are without adverse effects (Cordain et al. 2000).

Animal toxicity tests have shown that excessive intake of many of amino acids that are disproportionate to the normal diet composition, result in adverse events, including depression of food intake and growth (Garlick 2004). However, Tolerable Upper Intake Level (the highest level of a daily nutrient intake that is likely to pose no risk of adverse effects to most individuals) of individual amino acid has not been established in humans mainly due to insufficient scientific data (Hayashi 2003).

While several studies have demonstrated that a long-term intake of amino acids can improve insulin sensitivity and glucose metabolism among diabetic elderly persons (Solerte et al. 2004; Solerte et al. 2008a), others have suggested that a long-term dietary intake of high-dose amino acids or protein could cause insulin resistance and diabetes (Linn et al. 2000; Tremblay et al. 2005). Therefore, habitual supplementation with high-dosage amino acids should be considered with caution until further clinical studies on toxicity of amino acids are conducted in human.

CONCLUSIONS

Aging is associated with a progressive loss of muscle mass, which is most likely caused by the negative balance between muscle protein synthesis and protein breakdown rate. More evidence is accumulating which support the role of nutritional intake, especially protein and amino acids, in stimulating muscle protein anabolism regardless of age. However, insulin resistance specific to muscle protein metabolism is apparent with aging. Aging is also associated with a reduced anabolic response to amino acids and carbohydrate mixture, as well as amino acids themselves when given in a small quantity. However, more long-term clinical trials with larger sample size are needed to clarify the dietary protein requirement and to assess the specific amount of daily supplementation in preventing sarcopenia among the elderly population. Such dietary requirements should be defined specific to populations with different health, nutritional status, and daily physical activity level. Long-term clinical studies are also warranted to investigate the efficacy of combining exercise training with dietary supplement to maximize the anabolic response to prevent/delay the sarcopenia.

REFERENCES

Anthony, J.C., Anthony, T.G., Kimball, S.R., Vary, T.C. & Jefferson, L.S. 2000a. Orally administered leucine stimulates protein synthesis in skeletal muscle of postabsorptive rats in association with increased eIF4F formation. *J. Nutr.* 130(2): 139-145.

Anthony, J.C., Yoshizawa, F., Anthony, T.G., Vary, T.C., Jefferson, L.S. & Kimball, S.R. 2000b. Leucine stimulates translation initiation in skeletal muscle of postabsorptive rats via a rapamycin-sensitive pathway. *J. Nutr.* 130(10): 2413-2419.

Anthony, T.G., Anthony, J.C., Yoshizawa, F., Kimball, S.R. & Jefferson, L.S. 2001. Oral administration of leucine stimulates ribosomal protein mRNA translation but not global rates of protein synthesis in the liver of rats. *J. Nutr.* 131(4): 1171-1176.

Balagopal, P., Rooyackers, O.E., Adey, D.B., Ades, P.A. & Nair, K.S. 1997. Effects of aging on in vivo synthesis of skeletal muscle myosin heavy-chain and sarcoplasmic protein in humans. *Am. J. Physiol - Endocrinol Metab.* 273(4 Pt 1): E790-E800.

Bohe, J., Low, A., Wolfe, R.R. & Rennie, M.J. 2003. Human muscle protein synthesis is modulated by extracellular, not intramuscular amino acid availability: a dose-response study. *J Physiol.* 552(Pt 1): 315-24.

Boirie, Y., Dangin, M., Gachon, P., Vasson, M.P., Maubois, J.L. & Beaufrere, B. 1997. Slow and fast dietary proteins differently modulate postprandial protein accretion. *Proceedings of the National Academy of Sciences of the United States of America* 94(26): 14930-14935.

Boirie, Y., Gachon, P. & Beaufrere, B. 1997. Splanchnic and whole-body leucine kinetics in young and elderly men. *Am. J. Clin. Nutr.* 65(2): 489-495.

Campbell, W.W., Trappe, T.A., Wolfe, R.R. & Evans, W.J. 2001. The recommended dietary allowance for protein may not be adequate for older people to maintain skeletal muscle. *J. Gerontol. A. Biol. Sci. Med. Sci.* 56(6): M373-M380.

Carroll, C.C., Fluckey, J.D., Williams, R.H., Sullivan, D.H. & Trappe, T.A. 2005. Human soleus and vastus lateralis muscle protein metabolism with an amino acid infusion. *Am J Physiol. Endocrinol. Metab.* 288(3): E479-85.

Castaneda, C., Charnley, J.M., Evans, W.J. & Crim, M.C. 1995a. Elderly women accommodate to a low-protein diet with losses of body cell mass, muscle function, and immune response. *Am. J. Clin. Nutr.* 62(1): 30-9.

Castaneda, C., Dolnikowski, G.G., Dallal, G.E., Evans, W.J. & Crim, M.C. 1995b. Protein turnover and energy metabolism of elderly women fed a low-protein diet. *Am. J. Clin. Nutr.* 62(1): 40-48.

Cordain, L., Miller, J.B., Eaton, S.B., Mann, N., Holt, S.H. & Speth, J.D. 2000. Plant-animal subsistence ratios and macronutrient energy estimations in worldwide hunter-gatherer diets. *Am. J. Clin. Nutr.* 71(3): 682-92.

Dangin, M., Boirie, Y., Garcia-Rodenas, C., Gachon, P., Fauquant, J., Callier, P., Ballevre, O. & Beaufrere, B. 2001. The digestion rate of protein is an independent regulating factor of postprandial protein retention. *Am. J. Physiol - Endocrinol Metab* 280(2): E340-E348.

Dangin, M., Boirie, Y., Guillet, C. & Beaufrere, B. 2002. Influence of the protein digestion rate on protein turnover in young and elderly subjects. *J. Nutr.* 132(10): 3228S-3233S.

Dutta, C. & Hadley, E.C. 1995. The significance of sarcopenia in old age. *J. Gerontol. A Biol. Sci. Med. Sci.* 50 Spec No: 1-4.

Evans, W.J. 1990. What is sarcopenia? *J. Gerontol.* A Biol Sci Med Sci. 50 Spec No: 5-8.

Fiatarone, M.A., O'Neill, E.F., Ryan, N.D., Clements, K.M., Solares, G.R., Nelson, Me, Roberts S.B., Kehayias, J.J.,. Lipsitz, L.A & Evans, W.J. 1994. Exercise training and nutritional supplementation for physical frailty in very elderly people. *Engl. J. Med.* 330(25): 1769-1775.

Fiatarone, Singh, M.A., Bernstein, M.A., Ryan, A.D., O'Neill, E.F., Clements, K.M. & Evans, W.J. 2000. The effect of oral nutritional supplements on habitual dietary quality and quantity in frail elders. *J. Nutr. Health. Aging* 4(1): 5-12.

Food, B. Nutrition & M. Institute of 2002. Protein and Amino Acids. *Dietary Reference Intakes for Energy, Carbohydrates, Fiber, Fat, Protein and Amino Acids.* Washington, The National Academies Press**:** 465-608.

Frontera, W.R., Hughes, V.A., Lutz, K.J. & Evans, W.J. 1991. A cross-sectional study of muscle strength and mass in 45- to 78- yr-old men and women. *J. Appl. Physiol.* 71(2): 644-650.

Fujita, S., Rasmussen, B.B., Cadenas, J.G., Drummond, M.J., Glynn, E.L., Sattler, F.R. & Volpi, E. 2007. Aerobic exercise overcomes the age-related insulin resistance of muscle protein metabolism by improving endothelial function and Akt/mammalian target of rapamycin signaling. *Diabetes.* 56(6): 1615-1622.

Fujita, S., Rasmussen, B.B., Cadenas, J.G., Grady, J.J. & Volpi, E. 2006. Effect of insulin on human skeletal muscle protein synthesis is modulated by insulin-induced changes in muscle blood flow and amino acid availability. *Am. J. Physiol. Endocrinol. Metab.* 291(4): E745-E754.

Garlick, P.J. 2004. The nature of human hazards associated with excessive intake of amino acids. *J. Nutr.* 134(6 Suppl): 1633S-1639S; discussion 1664S-1666S, 1667S-1672S.

Hasten, D.L., Pak-Loduca, J., Obert, K.A. & Yarasheski, K.E. 2000. Resistance exercise acutely increases MHC and mixed muscle protein synthesis rates in 78-84 and 23-32 yr olds. *Am. J. Physiol.- Endocrinol & Metab.* 278(4): E620-E626.

Hayashi, Y. 2003. Application of the concepts of risk assessment to the study of amino acid supplements. *J. Nutr.* 133(6 Suppl 1): 2021S-2024S.

Holloszy, J.O. 2000. The biology of aging. *Mayo Clinic Proc.* 75 Suppl: S3-S8.

Katsanos, C.S., Chinkes, D.L., Paddon-Jones, D., Zhang, X.J., Aarsland, A. & Wolfe, R.R. 2008. Whey protein ingestion in elderly persons results in greater muscle protein accrual than ingestion of its constituent essential amino acid content. *Nutr. Res.* 28(10): 651-8.

Katsanos, C.S., Kobayashi, H., Sheffield-Moore, M., Aarsland, A. & Wolfe, R.R. 2005. Aging is associated with diminished accretion of muscle proteins after the ingestion of a small bolus of essential amino acids. *Am. J. Clin. Nutr.* 82(5): 1065-73.

Katsanos, C.S., Kobayashi, H., Sheffield-Moore, M., Aarsland, A. & Wolfe, R.R. 2006. A high proportion of leucine is required for optimal stimulation of the rate of muscle protein synthesis by essential amino acids in the elderly. *Am. J. Physiol. Endocrinol. Metab.* 291(2): E381-7.

Koopman, R., Verdijk, L.B., Beelen, M., Gorselink, M., Kruseman, A.N., Wagenmakers, A.J., Kuipers, H. & van Loon, L. J. 2008. Co-ingestion of leucine with protein does not further augment post-exercise muscle protein synthesis rates in elderly men. *Br. J. Nutr.* 99(3): 571-80.

Lexell, J. 1995. Human aging, muscle mass, and fiber type composition. *J. Gerontol. A. Biol. Sci. Med. Sci. 50 Spec No:* 11-16.

Linn, T., Santosa, B., Gronemeyer, D., Aygen, S., Scholz, N., Busch, M. & Bretzel, R.G. 2000. Effect of long-term dietary protein intake on glucose metabolism in humans. *Diabetologia* 43(10): 1257-65.

Melton, L.J., III, Khosla, S., Crowson, C.S., O'Connor, M.K., O'Fallon, W.M. & Riggs, B.L. 2000. Epidemiology of sarcopenia. *JAGS* 48(6): 625-630.

Paddon-Jones, D., Sheffield-Moore, M., Katsanos, C.S., Zhang, X.J. & Wolfe, R.R. 2006. Differential stimulation of muscle protein synthesis in elderly humans following isocaloric ingestion of amino acids or whey protein. Exp. Gerontol. 41(2): 215-9.

Paddon-Jones, D., Sheffield-Moore, M., Zhang, X.J., Volpi, E., Wolf, S.E., Aarsland, A., Ferrando, A.A. & Wolfe, R.R. 2004. Amino acid ingestion improves muscle protein synthesis in the young and elderly. *Am. J. Physiol - Endocrinol & Metab.* 286(3):E321-8.

Rasmussen, B.B., Fujita, S., Wolfe, R.R., Mittendorfer, B., Roy, M., Rowe, V.L. & Volpi, E. 2006. Insulin resistance of muscle protein metabolism in aging. *FASEB J.* 20(6): 768-769.

Reeds, P.J., Fjeld, C.R. & Jahoor, F. 1994. Do the differences between the amino acid compositions of acute-phase and muscle proteins have a bearing on nitrogen loss in traumatic states? *J. Nutr.* 124(6): 906-10.

Solerte, S.B., Fioravanti, M., Locatelli, E., Bonacasa, R., Zamboni, M., Basso, C., Mazzoleni, A., Mansi, V., Geroutis, N. & Gazzaruso, C. 2008a. Improvement of blood glucose control and insulin sensitivity during a long-term (60 weeks) randomized study with amino acid dietary supplements in elderly subjects with type 2 diabetes mellitus. *Am. J. Cardiol.* 101(11A): 82E-88E.

Solerte, S.B., Gazzaruso, C., Bonacasa, R., Rondanelli, M., Zamboni, M., Basso, C., Locatelli, E., Schifino, N., Giustina, A. & Fioravanti, M. 2008b. Nutritional supplements with oral amino acid mixtures increases whole-body lean mass and insulin sensitivity in elderly subjects with sarcopenia. *Am. J. Cardiol.* 101(11A): 69E-77E.

Solerte, S.B., Gazzaruso, C., Schifino, N., Locatelli, E., Destro, T., Ceresini, G., Ferrari, E. & Fioravanti, M. 2004. Metabolic effects of orally administered amino acid mixture in elderly subjects with poorly controlled type 2 diabetes mellitus. *Am. J. Cardiol.* 93(8A): 23A-29A.

Tinetti, M.E. & Williams, C.S. 1997. Falls, injuries due to falls, and the risk of admission to a nursing home. *New Eng. J. Med.* 337(18): 1279-1284.

Tremblay, F., Krebs, M., Dombrowski, L., Brehm, A., Bernroider, E., Roth, E., Nowotny, P., Waldhausl, W., Marette, A. & Roden, M. 2005. Overactivation of S6 kinase 1 as a cause of human insulin resistance during increased amino acid availability. *Diabetes* 54(9): 2674-84.

Verhoeven, S., Vanschoonbeek, K., Verdijk, L.B., Koopman, R., Wodzig, W.K., Dendale, P. & Van Loon, L.J. 2009. Long-term leucine supplementation does not increase muscle mass or strength in healthy elderly men. *Am. J. Clin. Nutr.* 89(5): 1468-75.

Volpi, E., Kobayashi, H., Mittendorfer, B., Sheffield-Moore, M. & Wolfe, R.R. 2003. Essential amino acids are primarily responsible for the amino acid-stimulation of muscle protein anabolism in healthy older adults. *Am. J. Clin. Nutr.* 78: 250-258.

Volpi, E., Mittendorfer, B., Rasmussen, B.B. & Wolfe, R.R. 2000. The response of muscle protein anabolism to combined hyperaminoacidemia and glucose-induced hyperinsulinemia is impaired in the elderly. *J. Clin. Endocrinol. Metab.* 85(12): 4481-4490.

Volpi, E., Mittendorfer, B., Wolf, S.E. & Wolfe, R.R. 1999. Oral amino acids stimulate muscle protein anabolism in the elderly despite higher first pass splanchnic extraction. *Am. J. Physiol. Endocrinol.Metab.* 277: E513-E520.

Volpi, E., Sheffield-Moore, M., Rasmussen, B.B. & Wolfe, R.R. 2001. Basal muscle amino acid kinetics and protein synthesis in healthy young and older men. *JAMA.* 286 (1206): 1212.

Welle, S., Thornton, C., Jozefowicz, R. & Statt, M. 1993. Myofibrillar protein synthesis in young and old men. *Am. J.Physiol.* 264: E693-E698.

Welle, S., Thornton, C. & Statt, M. 1995. Myofibrillar protein synthesis in young and old human subjects after three months of resistance training. *Am. J. Physiol. - Endocrinol & Metab.* 268: E422-E427.

Welle, S. & Thornton, C.A. 1998. High-protein meals do not enhance myofibrillar synthesis after resistance exercise in 62- to 75-yr-old men and women. *Am. J. Physiol.* 274(4 Pt 1): E677-E683.

Wolfson, L., Judge, J., Whipple, R. & King, M. 1995. Strength is a major factor in balance, gait, and the occurrence of falls. *J. Gerontology Series A-Biological Sci. Med. Sci.* 50 Spec No: 64-67.

Yarasheski, K.E., Zachwieja, J.J. & Bier, D.M. 1993. Acute effects of resistance exercise on muscle protein synthesis rate in young and elderly men and women. *Am. J. Physiol. Endocrinol. Metab.* 265: E210-E214.

Satoshi Fujita
College of Economics, Ritsumeikan University
1-1-1, Nojihigashi, Kusatsu, Shiga, 525-8577, Japan

Corresponding author: Satoshi Fujita
Email address: safujita@fc.ritsumei.ac.jp
Tel: +81-77-561-5229; Fax: +81-077-561-3761

Received: April 2009
Accepted for publication: June 2009

0