ISSN: 2414-1895 DOI: 10.6919/ICJE.202102_7(2).0056

The Role of Leucine in Cancer Cachexia Treatment

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Abstract

This passage develop the hypothesis that Cancer Cachexia patients consuming supplements with Leucine would reduce the symptoms of Cachexia including malnutrition (lack of nutrition), weight lost and a shorter survival time. Approximately 50% of people with cancer will have Cachexia; so, it is important to pay attention to Cachexia and find a Treatment solving it since it also helps recover or control the patients' condition in cancer. Leucine play an important role in balancing the creation and decomposition of protein that help with maintain muscle structure. The leucine metabolite β-hydroxy-β-methylbutyric (HMB), created by leucine, can activates the signaling connection between protein synthesis and skeletal muscle growth, even promotes muscle regeneration. This means leucine can possiblly be used in studying Cancer Cachexia Treatment and improving cancer patient's health. In this study, tests are run out on NMRI mice(common experimental animal in biology also develops a wide variety of spontaneous tumors while ageing) that are at different stages(1-5) of MAC16 adenocarcinoma (which is a kind of tumor typically found in NMRI mice to see consuming more leucine can positively affect cancer muscle atrophy and become one of the optional treatment of Cachexia.

Keywords

Leucine Metabolite β-Hydroxy-β-Methylbutyrate(HMB); Muscle Wasting; Skeletal Muscle; Protein Breakdown; Proteasomes.

1. Introduction

Cancer patients often suffer from different types of cancer complications; usually cancer patients, especially advanced cancer patients, will look weaker or even thinner than normal people, because these patients are usually affected by cancer cachexia. Usually, cachexia [1] manifests itself as extremely thin, skinny, shaped like a skull, anemia, and weakness. Studies have shown that about half of cancer patients have this cancer syndrome [2], and at the same time this syndrome is also the cause of death for 20% of cancer patients. [3] Cancer patients usually begin to show poor nutrition, and severely reduced muscle mass at various stages of cancer. Obviously, this has no benefits for the health, cancer treatment and immunity of cancer patients.

In recent years, there are many literatures that have emphasized the positive effects of branched-chain amino acids on cancer cachexia, especially leucine, so take this opportunity to learn more about how leucine can help improve low muscle mass and muscle atrophy.

Leucine is one of the branched Amino Acids (BCAA). BCAA includes leucine, isoleucine, and valine. BCAA is by far the largest amount of essential amino acids for food, comprising about 35% essential amino acids for muscle protein and about 40% essential amino acids for mammals. In our bodies, leucine is catalyzed by BCAA transaminase to produce -keto isohexyl acid, a type of branched keto acid. Then, irreversible oxidative decarboxylation of -ketone isocaproic acid catalyzed by BCAA dehydrogenase results in ketoacid and acetyl-CoA (CoA) derivatives with one carbon atom less. Eventually, it breaks down to acetoacetic acid and acetyl CoA into the citric acid cycle.(Figure 1)

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BCAA promotes nitrogen storage and protein synthesis. Leucine can regulate protein metabolism, while isoleucine and valine have no significant effect on protein synthesis and degradation. Leucine is the only amino acid that can regulate protein turnover in skeletal muscle and myocardium. It can promote the synthesis of skeletal muscle protein without affecting its degradation. Leucine increases protein synthesis by up to 50% and inhibits protein decomposition by only 25%. The metabolites of leucine -ketopentanoic acid (-KIC) and -hydroxy--methyl-butyric acid (HMB) can regulate protein metabolism. Leucine inhibition of decomposition mainly through -KIC to promote the secretion of insulin, inhibit glucagon secretion, thereby inhibiting glycogenosis, slow down the breakdown of muscle protein.[4,5]

This experiment is designed based on the characteristics and the function in our body. By considering the symptom of cancer cachexia with the effect of leucine, this study come out the idea and an experiment on mice for testing a possible treatment that could reduce some of the symptom of cachexia.

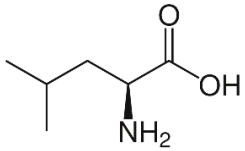

Figure 1. Leucine Chemical Figure

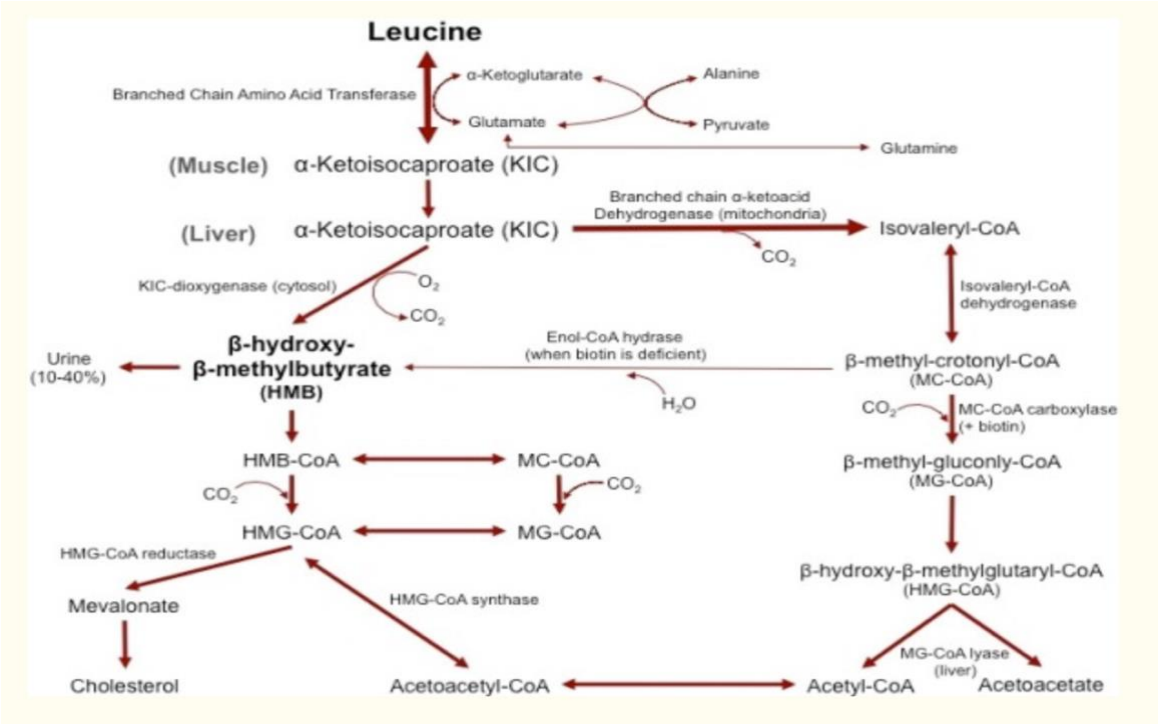

Figure 2. Leucine transferase [4]

2. Experimental Subjects and Methods

2.1 Material:

MAC16 Tumor Fragments (A typical tumor that can be found in NMRI mice)

NMRI mice [6] (common experimental animal in Biology also develops a wide variety of spontaneous tumors while ageing)

Weighting Scales

Leucine

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2.2 Method:

First, the experiment will transplanting the fragments of the Mac Tumor in the NMRI mice that was selected and cultured to different stages of cancer (1-5) And then only use the mice that have Cachexia in the experiment.

The actual experience will last two days, during the two days of the experiment, all mice will have extra Leucine powder in their food. Before the experiment finally start, all mice are eating and drinking normal food and water. The mice will be weighted 4 times during 2 days of the experiment,1 time before, 1 time in at the end of each day's experiment, and one more time after two days of experiment. Every mouse will also take a measurements of proteasome activity before and after the experiment. And all the data will be collected for future comparison and study.

2.3 Measurement of Proteasome Activity.

The functional activity of the proteasome is determined by measuring the chymotrypsin-like enzyme activity (the main proteolytic activity of the proteasome subunit) [7] We will use this method to test out the functional activity of the proteasome.

2.4 Animal Model:

The mice with cancers cachexia will be separate from different stage of their cancer from 1-5. Each mice will be weighed 4 times in the entire experiment and 2 measurement of proteasome activity. Their weight and the result of Proteasome activity before the experiment will be compared with the result after the experiment.

2.5 Possible Results of the NMRI Mice experiment

Result 1: Most of NMRI Mice with Cachexia continued to lose weight, and the situation did not improve after consuming more Leucine.

Result 2: NMRI Mice with Cachexia in early stage of cancer show more signs on stop/decline the speed of losing weight and muscle after consuming more Leucine.

Result 3: NMRI Mice with Cachexia show signs stop/decline the speed of losing weight and muscle after consuming more Leucine, but it is totally ramdom(It is totally random in stage).

Result 4: All NMRI mice from the experimental have positive reflection on the grow/contain muscle and/or stop the sign of losing weight.

Table 1. Possible Results

	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Result 1	-	-	-	-	-
Result 2	+	+	?	-	-
Result 3	+	-	-	-	+
Result 4	+	+	+	+	+

* + indicates:Improvement has occurred on most of the NMRI mice(at that stage).

* - indicates: No obvious improvement was occurred on most of the NMRI mice(at that stage).

* ? indicates: The result cannot tell if the treatment is effective or not by just looking at the result.

2.6 Discussion

Studies have shown that Branch-Chain Amino Acids (BCAA, Including Leucine, isoleucine, and valine) is the substrates for protein production, but also stimulatory effect on protein production and an inhibitory effect on proteolysis [5]. In this study, only mice could take the leucine. It does not contain other Amino Acid, so it is possible to better observe Leucine's role in promoting overall protein synthesis when treating Cachexia.

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Results 1 raised the possibility that this experiment failed. After two days of Leucine, Cachexia did not improve in all (mostly) tumor mice, muscle fat still declined, and the mice did not gain weight. This suggests that treating Leucine as a treatment for Cachexia in mice will not work. If you take too much Leucine, the extra Leucine will not promote muscle formation.

The second result raised the possibility that Leucine was more effective in early cancer Cachexia mice. When different tumor mice were given Leucine, only early tumor mice were controlled: muscle loss/weight loss improved. The reason for this has to do with the health of the mice themselves, and Leucine may not be able to do much with Cachexia Treatment when cancer spreads through the mice.

Results 3 showed that after 2 days of Leucine administration, NMCI tumor mice showed corresponding improvement over the same period, but in a random state, no pattern was found. The reason for this result may be that the number of mice in the experimental group is not large enough to produce a good result. It could also be that different mice have different abilities to absorb Leucine.

If the results 4 were shown-all the Cachexia symptoms were altered, muscle loss and weight loss slowed or even resumed. This suggests that Leucine has the degradation of muscle tissue by increasing the synthesis of muscle proteins, and further confirms that Leucine can help patients with different stages of cancer maintain or even gain weight and muscle fiber. There are other studies shows similar result. [8,9]

3. Conclusion

Overall, this study discussed all possible effects of Leucine on NMRI mice with MAC16tumor and marked Cachexia symptoms. This study further discusses how these cancer mice behaved differently when given Leucine at different times and study adds to the evidence that giving patients with cancer Cachexia moderate doses of Leucine is beneficial for their cancer treatment and recovery. This research may enable cancer patients to start taking Leucine even before the symptoms of Cachexia develop, so that they can help prevent future health risks with Cachexia. In the future, taking Leucine may not be the best option for improving/treating Cachexia because the study may not present the body burden/risk of overdose, but Leucine is not a bad option at this point. More experience should be develop: the amount of leucine the patient should consume, negative effect of this treatment, any replaceable or similar product etc.

References

[1] Tisdale, M.J., Mechanisms of Cancer Cachexia. Physiological Reviews, 2009. 89(2): p. 381-410.

[2] Inui, A., Cancer Anorexia-Cachexia Syndrome: Current Issues in Research and Management. CA: A Cancer Journal for Clinicians, 2002. 52(2): p. 72-91.

[3] Martignoni, M.E., P. Kunze, and H. Friess, Cancer cachexia. Molecular Cancer, 2003. 2(1): p. 36.

[4] Wilson, J.M., et al., International Society of Sports Nutrition Position Stand: beta-hydroxy-beta-methylbutyrate (HMB). Journal of the International Society of Sports Nutrition, 2013. 10(1): p. 6-6.

[5] Holeček, M., Branched-chain amino acids in health and disease: metabolism, alterations in blood plasma, and as supplements. Nutrition & metabolism, 2018. 15: p. 33-33.

[6] Monitto, C.L., et al., Differential gene expression in a murine model of cancer cachexia. Am J Physiol Endocrinol Metab, 2001. 281(2): p. E289-97.

[7] Orino, E., et al., ATP-dependent reversible association of proteasomes with multiple protein components to form 26S complexes that degrade ubiquitinated proteins in human HL-60 cells. FEBS Letters, 1991. 284(2): p. 206-210.

[8] Smith, H.J., P. Mukerji, and M.J. Tisdale, Attenuation of proteasome-induced proteolysis in skeletal muscle by {beta}-hydroxy-{beta}-methylbutyrate in cancer-induced muscle loss. Cancer Res, 2005. 65(1): p. 277-83.

[9] Le Bricon, T., et al., Supplemental Nutrition with Ornithine α-Ketoglutarate in Rats with Cancer-Associated Cachexia: Surgical Treatment of the Tumor Improves Efficacy of Nutritional Support. The Journal of Nutrition, 1995. 125(12): p. 2999-3010.