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Young V R & Munro H N. N^{τ}-methylhistidine (3-methyl histidine) and muscle protein turnover: an overview. *Fed. Proc.* 37:2291-300, 1978.
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This review integrates almost 10 years of work exploring the use of N^{τ}-methylhistidine (3-MeHis) as an indicator of the in vivo degradation rate of muscle contractile proteins. It has received wide use in clinical catabolic states. [The *SCI*® indicates that this paper has been cited in more than 365 publications.]

Index of Muscle Protein Degradation

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The paper is a review of N^{τ}-methylhistidine (3-MeHis) as a way of measuring the breakdown rate of muscle contractile proteins. It was first presented at a symposium in Chicago in 1977. The symposium is memorable for water dripping from the ceiling and landing on speakers' podium in increasingly menacing quantities, threatening to terminate the proceedings prematurely. This moved the chairman (H.N. Munro) to comment that the room above must have housed a convention of urologists!

In the early 1940s, R. Schoenheimer used isotopically labeled amino acids to show that tissue proteins turn over at different rates. Subsequent attempts to quantify in vivo turnover rates of body proteins were frustrated by reincorporation of the labeled amino acids. The rate of breakdown could be resolved if a nonreutilizable amino acid was released and completely excreted in the urine. In the late 1960s, Vernon R. Young was contributing a chapter on muscle protein metabolism for the fourth volume of the now-classic series *Mammalian Protein Metabolism*[1] and was intrigued by the possibility that 3-MeHis might fulfill this role. Similarly, Munro was impressed by the lack of interest in 3-MeHis. We agreed to work together and soon showed that breakdown of muscle proteins resulted in release of 3-MeHis which was not reutilized for protein synthesis.[2] This was confirmed when ^{14}C-labeled 3-MeHis was administered to rats and to humans with recovery of nearly 100 percent within two to three days. Since the major reservoir of protein-bound 3-MeHis was skeletal muscle,[3] urinary output of 3-MeHis was considered to reflect the amount of skeletal muscle and its turnover rate. Some 3-MeHis arises from the turnover of actin in other tissues, especially the intestinal tract, and this can complicate interpretation of the metabolic significance of changes in urinary MeHis. Nevertheless, the output of 3-MeHis via urine was measured for studying various factors involving muscle protein balance, especially in human subjects where the intestinal contribution is low.[4] It was shown that aging reduced the output of 3-MeHis, which was compatible with the loss of muscle mass in the elderly. Further, it was demonstrated that urinary 3-MeHis output was reduced by chronic restriction of dietary proteins and/or energy in growing rats and also in malnourished infants in India—a response that could be reversed by providing appropriate intakes of protein and energy.

After the 1978 review, some hormones were found to affect urinary output of 3-MeHis; thyroxine within the normal range of thyroid gland activity affected 3-MeHis output whereas corticosterone increased 3-MeHis output at hormone levels equivalent to severe stress. Diabetes in rats increased 3-MeHis output which could be corrected by insulin administration.

Additional areas of application have also emerged. In a number of species, the muscles contain significant amounts of balenine (3-methyl-histidine-β-alanine), which may divert the fate of labeled 3-MeHis. For human studies, a diet free of meats for a few days is needed to eliminate an exogenous source of urinary 3-MeHis. However, as J. Sjolin et al.[5] pointed out, the peptide anserine (1-methyl histidine-β-alanine) occurs in the muscles of most vertebrates, but not in human muscles. So the urinary output of 1-MeHis can be used to estimate the amount of meat consumed and, thus, the 3-MeHis that originates from the diet. Overall, the measurement of 3-MeHis has proved to be a valuable marker of muscle protein breakdown in isolated muscle preparations and in vivo studies.

1. **Young V R.** The role of skeletal and cardiac muscle in the regulation of protein metabolism. (Munro H N, ed.) *Mammalian protein metabolism.* New York: Academic Press, 1970. Vol. 4. p. 585-674. (Cited 170 times.)
2. **Young V R, Alexis S D, Baliga B S, Munro H N & Muecke W.** Metabolism of administered 3-methylhistidine. Lack of muscle transfer ribonucleic acid charging and quantitative excretion as 3-methylhistidine and its N-acetyl derivative. *J. Biol. Chem.* 247:3592-600, 1972. (Cited 255 times.)
3. **Haverberg L N, Omstedt P T, Munro H N & Young V R.** N^{τ}-methylhistidine content of mixed proteins in various rat tissues. *Biochim. Biophys. Acta* 405:67-71, 1975. (Cited 130 times.)
4. **Sjolin J, Stjernstrom H, Hennenberg S, Anderson E, Mårtensson J, Friman G & Larsson J.** Splanchnic and peripheral release of 3-methylhistidine in relation to its urinary excretion in human infection. *Metabolism* 38:23-9, 1989.
5. **Sjolin J, Hjort G, Friman G & Hambraeus L.** Urinary excretion of exogenous 3-methylhistidine and intake of meats from various sources. *Metabolism* 36:1175-84, 1987.

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