findings to humans is potentially of great clinical significance for both maternal health and childhood development. NR has been shown to be well tolerated and is generally considered safe as a dietary supplement in humans [9,10]. However, future clinical trials are needed to determine the potentially exciting benefits of NR at the maternal–offspring interface.

Acknowledgments

Y.W. is Lawrence Raiz Professor in Bone Cell Metabolism and a Virginia Murchison Lithicium Scholar in Medical Research. This work was in part supported by The Welch Foundation (I-1751, Y.W.), NIH (R01CA238487, R01CA236802, Y.W.), CPRIT (RP180047, Y.W.), DOD (W81XWH-18-1-0014, Y. W.) and UTSW Endowed Scholar Startup Fund (Y. W.). The authors declare that they have no financial conflict of interest.

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Spotlight

Anticatabolic Effects of Ketone Bodies in Skeletal Muscle

Andrew P. Koutnik,1 Dominic P. D’Agostino,1 and Brendan Egan 2,2,*

The ketone bodies acetoacetate (AcAc) and β-hydroxybutyrate (βHB) are the subject of renewed interest given recently established pleiotropic effects regulating inflammation, oxidative stress, and gene expression. Anticatabolic effects of β-hydroxybutyrate have recently been demonstrated in human skeletal muscle under inflammatory insult, thereby expanding upon the wide-ranging therapeutic applications of nutritional ketosis.

AcAc, βHB, and acetone are lipid-derived ketone bodies whose production is amplified through ketogenesis during fasting, starvation, and carbohydrate restriction [1]. Metabolic effects of AcAc and βHB in many organs are well established, including anticatabolic processes such as attenuation of glycolysis, hepatic glucose output, and adipose tissue lipolysis [1]. Among more recent discoveries are the pleiotropic effects of βHB as a signaling metabolite regulating oxidative stress, inflammation, and gene expression [2]. Renewed scientific interest into the therapeutic and performance potential of ketone bodies has emerged with the development of ingestible exogenous ketone supplements [3]. These compounds rapidly induce nutritional and/or therapeutic ketosis without dietary restriction.

A growing area of interest is the anabolic and anticatabolic potential of ketone bodies in skeletal muscle provided by therapeutic ketosis. Thomsen and colleagues [4] have recently made a significant contribution to this paradigm by examining both the anticatabolic and anabolic potential of βHB in human skeletal muscle under an acute inflammatory insult provided by lipopolysaccharide (LPS) endotoxin. This is salient because with aging, cancer, HIV/AIDS, chronic heart and renal failure, chronic obstructive pulmonary disease, and rheumatoid and osteoarthritis, dramatic losses in muscle mass and function are often observed. Additionally, a pathological decline in skeletal muscle health is not only a strong predictor of mortality, but also predicts a reduced ability to receive, tolerate, and respond to disease burden and/or standard of care therapies [3]. However, with minimal to no anticatabolic therapeutic options, novel mitigation strategies are critical for altering disease course and improving patient outcomes.

Therapeutic strategies for skeletal muscle health primarily address muscle protein turnover; the continuous process of synthesis and degradation of skeletal muscle proteins. The balance between the rates of muscle protein synthesis (MPS) and degradation (muscle protein breakdown; MPB) determines changes in skeletal muscle mass in both acute and long-term scenarios. Inflammation is a primary factor and/or underlying characteristic of many atrophy-related conditions, including those impacting on skeletal muscle, likely through augmenting MPB, and/or attenuating MPS (Figure 1).
Ketone bodies were long-hypothesized to be protein sparing, or anticatabolic, because experimentally elevating ketone bodies improved nitrogen balance (a proxy for muscle protein turnover) under catabolic conditions including post-surgery, skeletal trauma, severe burns, and sepsis [6]. Additionally, the anabolic potential of βHB, at least in healthy men, was demonstrated by the infusion of sodium βHB to ~2 mM which attenuated leucine oxidation and increased MPS by ~10% [7], with analogous anabolic effects reported in post-exercise feeding in humans, in myotubes in vitro, and muscle injury models in rodents [3].

These promising data, in concert with the aforementioned effects of ketone bodies reducing inflammation and oxidative stress, leads to the hypothesis that ketone bodies may have anticatabolic and/or anabolic effects during inflammation-related muscle atrophy. To test this hypothesis, Thomsen et al. [4] used LPS as an acute inflammatory stimulus to ten healthy, overnight-fasted, men. LPS rapidly induces weight loss in both skeletal muscle and adipose tissue compartments via established disease-induced catabolic pathways. However, Thomsen et al. focused on the first 6 h after insult using labeled tracers and muscle biopsy sampling to measure protein kinetics and intracellular signaling pathways under separate occasions of infusion of (i) saline, (ii) lipids to elevate free fatty acid concentrations, and (iii) sodium D/L-βHB, which produced circulating βHB concentrations of ~3.5 mM. These effects were investigated under fasting (basal; 4 h), and insulin-stimulated (hyperinsulinemic–euglycemic clamp; 2 h) conditions. Uniquely, acipimox, a niacin derivative that inhibits lipolysis via hydroxycarboxylic acid receptor 2 (HCA2) signaling, was provided in all conditions in order to control the influence of altered free fatty acid concentrations as a confounding factor between conditions.

Under these conditions, βHB produced a robust anticatabolic response, as indicated by a 70% reduction in phenylalanine efflux from muscle (and confirmed by other tracer kinetic measurements), even though systemic inflammation was higher in this condition compared to controls. The anticatabolic effect of βHB was only slightly enhanced under hyperinsulinemia, and the absence of βHB was unable to reduce phenylalanine efflux with hyperinsulinemia alone. This
suggests that βHB is a more potent anti-catabolic stimulus than hyperinsulinemia in this model, and supports the hypothesis that βHB could exert antitrophic effects in inflammation-driven muscle atrophy.

However, contrary to the previous observation of anabolic effects of βHB on skeletal muscle, Thomsen et al. observed that βHB may, in fact, attenuate MPS under this inflammatory insult. However, an attenuation of MPS is perhaps unsurprising given the association of inflammation and elevations in inflammatory cytokines with anabolic resistance in skeletal muscle [8]. The elevation in βHB concentrations produced by Thomsen et al. failed to suppress the stimulation of cytokine production including interleukin (IL)-1β, which the authors hypothesized based on the recently described anti-inflammatory effect of βHB [9]. In that work, LPS-mediated activation of the NLRP3 inflammasome and IL-1β production by macrophages was attenuated by βHB. The model employed by Thomsen et al. is a rather different in vivo physiological context in which βHB infusion was unable to sufficiently mitigate the inflammatory response. In particular, the use of acipimox may have introduced competition for the HCAR2 receptor through which βHB also acts. Additionally, endotoxemia results in nitration and inactivation of succinyl-CoA:3-oxoacid CoA transferase (OXCT1) [10], the rate limiting enzyme in ketolysis and subsequent ketone utilization in extrahepatic tissues. Combined, these two mechanisms may have reduced the activity, and therefore metabolic effects, of βHB in selected tissues.

Ultimately, muscle atrophy results from either a decline in the rate of MPS, an increase in the rate of MPB, or a simultaneous decline in MPS in combination with an increase in MPB. Overall, muscle atrophy requires that MPS is repressed relative to MPB. Thomsen et al. [4] highlighted an antitrophic effect of βHB, which, even in the presence of a degree of anabolic resistance consequent to inflammatory insult, elicited a net positive protein balance in skeletal muscle under these catabolic conditions. Looking forward, it will be intriguing to discover if the implications of these findings reach beyond LPS-mediated inflammation into subclinical (e.g., disuse atrophy, sarcopenia) and/or overt (e.g., cachexia) inflammation-induced skeletal muscle atrophy pathologies. Considering the increasing evidence for therapeutic ketosis and the emergent ability to easily and safely administer exogenous ketones, benefits in tissues beyond skeletal muscle atrophy pathologies may also be realized.

**Disclaimer Statement**

B.E. declares no competing interests. D.D. is an inventor on a patent entitled ‘Composition and methods of elevating and sustaining ketosis’ United States Patent and Trademark Office (USPTO) 20170266148. This invention was made with government support under Grant number N00014-13-1-0062 awarded by the Department of Defense, Office of Naval Research. A.K. and D.D. are inventors on provisional patents ‘Compositions and methods for weight loss management’ and ‘Prevention of muscle wasting with Ketone supplementation’. At the time of this publication, provision patents were still under review. However, should provisional patents become accepted and royalties ever accrue, A.K. and D.D. will receive a share under the terms prescribed by the University of South Florida. D.D. is an owner of Ketone Technologies LLC.

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https://doi.org/10.1016/j.tem.2019.01.006

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**References**


**Spotlight**

**ACMSD: A Novel Target for Modulating NAD⁺ Homeostasis**

Jun Yoshino1,*

NAD⁺ has a pivotal role in regulating many biological processes. A recent study (Palzer et al., *Cell Rep.* 2018, 25;1359–1370) demonstrated that alpha-amino-beta-carboxy-muconate-semialdehyde decarboxylase (ACMSD) is a key regulator of NAD⁺ metabolism and overexpression of human ACMSD leads to niacin dependency for NAD⁺ biosynthesis in mice, providing important insights into human diseases associated with niacin/NAD⁺ deficiency.

NAD⁺ is an important redox coenzyme found in all species. Recent studies