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Multisystem Regulatory Capacity of Exogenous Ketone Administration at Rest

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Acute ingestion of exogenous ketone supplements (EKS) in the form of a (R)-3-hydroxybutyl (R)-3-hydroxybutyrate (R-BD R-βHB) ketone monoester (KME) has demonstrated the ability to alter metabolism and acid/base balance at rest. **PURPOSE:** To explore how a variety of new, yet unstudied, forms of commercially-available EKS modulate metabolism and acid/base balance pharmacokinetics at rest. **METHODS:** Utilizing a single-blind, placebo-controlled, randomized crossover design, twenty healthy participants (M: 10, F:10; age: 20.6±2.0 y, height: 171.7±7.5 cm, weight: 67.9±10.2 kg) visited the laboratory on 5 separate occasions, comprising one familiarization and four main experimental sessions with ≥7-day wash-out period between experimental sessions. The four main experimental sessions (visits 2 to 5) consisted of metabolic, cardiac (autonomic & hemodynamic), blood gases (acid-base & gas exchange) and cognitive evaluation at rest measured at various time points. The visits differed only in the randomly assigned drink consumed, which included various EKS (395 mg/kg), namely KME, KME+sodium bicarbonate (KME+BIC), and a non-racemic ketone salt (KS), and were compared to a non-caloric taste-matched placebo (PLA). **RESULTS:** All EKS significantly increased blood R-βHB concentration (30 min, KME: 2.6±0.7 mM; KME+BIC: 3.2±0.9 mM; KS: 1.5±0.4 mM; all $p<0.001$) and reduced blood glucose concentration (30 min, KME: -15.8±14.7 mg/dL, $p<0.01$; KS: -11.6±10.3 mg/dL, $p<0.05$) compared to PLA. KME ingestion decreased pH (-0.04±0.03, $p<0.001$), whereas KS (60 min, 0.03±0.03, $p<0.05$) and KME+BIC (120 min, 0.05±0.05, $p<0.001$) increased pH compared to PLA. Cognitive performance during the Stroop color word test and switching task did not differ at any time point within or between conditions (all $p>0.05$). **CONCLUSION:** Exogenous ketosis produced by the ingestion of KS or KME alone (~2-4 mM) does not affect indirect calorimetry, HRV, hemodynamics, or cognition at rest in young healthy males and females. KME+BIC increased the degree of ketosis (~0.5 mM), altered HRV, and increased pH. The non-racemic KS produced a more rapid and higher peak blood ketone concentration compared to previous work in racemic KS, suggesting that such formulations warrant further investigations. **SIGNIFANCE/NOVELTY:** A novel finding is that a non-racemic KS increased blood R-βHB concentration >2.0 mM. This finding warrants future work into comparing KME and non-racemic KS at similar concentrations of EKs to elucidate any further differences or best application for either exogenous ketone source.

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