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Comprehensive Review of Studies on β-Aminoisobutyric Acid (BAIBA)

Introduction

β-Aminoisobutyric Acid (BAIBA) is a non-proteinogenic amino acid produced during thymine and valine catabolism and exists as two enantiomers: L-(S)-BAIBA and D-(R)-BAIBA. BAIBA has gained prominence as a myokine—an exercise-induced molecule released from skeletal muscle—and as a potential biomarker and therapeutic agent. Exercise increases BAIBA secretion, and evidence shows BAIBA influences lipid metabolism, glucose homeostasis, bone formation, inflammation, oxidative stress and cardiovascular health. Studies span animal models, human clinical trials, epidemiological analyses and in vitro research. Below is a detailed summary of every study found on PubMed that references BAIBA through 2025.

Metabolism and Analytical Studies

Metabolism of BAIBA and Inborn Errors of Pyrimidine Degradation

- **Pyrimidine degradation (1997)** – A review explained that uracil degradation produces β-alanine, whereas thymine is degraded to the R-(−)-BAIBA enantiomer; aminotransferases are required to convert BAIBA and γ-aminobutyric acid into acetoacetate or succinyl-CoA [1]. Defects in these enzymes cause accumulation or deficiency of metabolites, emphasising the clinical importance of identifying inborn errors of pyrimidine metabolism and exercising caution with pyrimidine-analogue chemotherapy [1].

- **Urinary BAIBA in cancer (1973-1987)** – Early clinical studies observed elevated urinary BAIBA in patients with leukaemia, lymphoma and other malignancies. The 1987 study concluded that urinary BAIBA and the BAIBA/uric-acid ratio were increased in many cancer patients; the authors suggested these elevations reflected thymine catabolism and tissue turnover rather than renal dysfunction [2]. These early findings linked BAIBA excretion to nucleic-acid breakdown.

Analytical Methods for BAIBA

- **LC-MS/MS deconvolution (2017)** – Scientists developed an LC-MS/MS method combining Gaussian and linear deconvolution to separate eight aminobutyric acid isomers, including D- and L-BAIBA [3]. Human serum analysis revealed ~0.8 μM L-BAIBA and trace amounts of D-BAIBA [3].

- **Quantification of aminobutyric acids (2020)** – An LC-MS method measured D-BAIBA, L-BAIBA and γ-aminobutyric acid in plasma. D-BAIBA and GABA positively correlated with physical activity and hip bone mineral density in young lean women, while D-BAIBA correlated with hip BMD in older adults without osteoporosis [4]. These findings proposed BAIBA and GABA as potential biomarkers for osteoporosis.

- **Dose-response pharmacokinetics (2023)** – A crossover trial in healthy adults assessed plasma BAIBA after oral L-BAIBA doses (250–1500 mg). Peak concentrations and area under the curve increased dose-dependently without adverse effects [5]. The study confirms BAIBA's safety and provides dosing data for future supplementation trials.

BAIBA as an Exercise-Derived Myokine

Discovery and Metabolic Effects

- **Myokine identification (Cell Metab 2014)** – Metabolomic profiling of mice overexpressing PGC-1α identified BAIBA as a small-molecule myokine induced by exercise. BAIBA treatment stimulated expression of brown-fat genes in white adipose tissue and increased fatty-acid β-oxidation in hepatocytes via PPARα activation [6]. In mice, BAIBA improved glucose tolerance and induced a brown-like phenotype in mesenchymal stem cells, while human plasma BAIBA levels increased with exercise and inversely correlated with metabolic risk factors [6].

- **Skeletal muscle secretion and insulin secretion (Metabolism Open 2020)** – Human studies demonstrated that skeletal muscle releases BAIBA at rest and during aerobic exercise. Immobilisation suppressed BAIBA release. Plasma BAIBA negatively associated with insulin secretory function, and in insulin-secreting INS-2 832/3 cells BAIBA reduced mitochondrial energy metabolism and insulin secretion [7]. These results indicate BAIBA may act as a myokine influencing pancreatic β-cells.

- **Exercise increases BAIBA enantiomers (Front Physiol 2019)** – Acute cycling exercise increased plasma concentrations of both R-(D)-BAIBA and S-(L)-BAIBA (20 % and 13 %, respectively) in healthy adults [8]. Baseline R-BAIBA levels were much higher than S-BAIBA and were strongly influenced by the AGXT2 rs37369 polymorphism [8], indicating that BAIBA enantiomers have distinct metabolic origins.

- **Low-calorie diet and exercise (Front Physiol 2023)** – Women with obesity following a low-calorie diet with or without interval exercise showed increased BAIBA levels, decreased weight and leptin concentrations, and improved insulin sensitivity. Higher BAIBA correlated with greater weight loss, reduced leptin, and improved hepatic insulin clearance [9]. The findings suggest that an energy deficit (diet) is a key regulator of BAIBA.

Animal Evidence of Metabolic and Cardioprotective Effects

- **Prevention of diet-induced obesity (Obesity 2008)** – Chronic BAIBA administration (100 mg/kg/day) to leptin-deficient (ob/+) mice fed a high-calorie diet prevented weight gain, steatosis, necroinflammation and glucose intolerance. BAIBA increased hepatic fatty-acid oxidation, carnitine palmitoyltransferase-1, and phosphorylated acetyl-CoA carboxylase while reducing de novo lipogenesis [10]. BAIBA also restored plasma leptin levels, suggesting improved leptin secretion [10].

- **Oct-B derivative (Biochem Biophys Res Commun 2024)** – A BAIBA ester called Oct-B exhibited ~80-fold greater potency than L-BAIBA in reducing high-fat diet-induced obesity in mice. Oct-B lowered serum triglycerides, cholesterol and LDL, decreased hepatic lipid accumulation, upregulated

thermogenic genes and increased tissue BAIBA levels [11]. This derivative may represent a potent anti-obesity agent.

- **BAIBA prevents leptin deficiency–associated obesity (2010)** – A review summarised early evidence that BAIBA, produced during thymine catabolism, increases fatty-acid oxidation and leptin production from white adipose tissue, thereby reducing body weight and improving lipid homeostasis [12]. The authors proposed BAIBA as a pharmacological strategy for obesity prevention.

- **Cardioprotection via miR-208b/AMPK (Front Cardiovasc Med 2022)** – Exercise increased BAIBA levels in rats with heart failure; BAIBA treatment produced cardioprotective effects similar to exercise by up-regulating miR-208b and activating AMPK. BAIBA reduced metabolic stress and apoptosis in cardiomyocytes, and the protective effects were abolished by AMPK inhibition [13]. These findings identify the miR-208b/AMPK pathway as a mechanism for BAIBA's cardioprotective actions.

- **Neuroprotection through AMPK/PI3K/Akt (IBRO Neurosci Rep 2021)** – In PC12 cells, L-BAIBA increased AMPK and Akt phosphorylation; pretreatment suppressed H_2O_2-induced ROS generation and apoptosis. Inhibition of AMPK or PI3K/Akt abolished the protective effect, indicating that BAIBA prevents oxidative stress via these pathways [14].

Bone and Muscle Crosstalk

- **Osteocyte survival factor (Cell Rep 2018)** – Exercise increased BAIBA production in mice, and BAIBA acted as a muscle-derived osteocyte survival factor. L-BAIBA prevented osteocyte apoptosis via the MRGPRD receptor and preserved mitochondrial integrity [15]. BAIBA supplementation in drinking water prevented bone and muscle loss, but this protective effect decreased with age due to reduced Mrgprd expression [15].

- **FGF23 regulation (Cell Rep 2024)** – Both L- and D-BAIBA increased fibroblast growth factor 23 (FGF23) production in osteocytes via the MRGPRD receptor. L-BAIBA signalled through Gαs/cAMP/PKA/CBP/β-catenin and Gαq/PKC/CREB pathways, while D-BAIBA acted indirectly via sclerostin and Gαi/NF-κB signalling [16]. These distinct pathways converge to increase urinary phosphate excretion after exercise.

- **Exercise and osteoclastogenesis (J Sport Health Sci 2025)** – In ovariectomized mice, exercise increased L-BAIBA levels, suppressed osteoclastogenesis and prevented bone loss. L-BAIBA supplementation replicated these effects. Mechanistically, L-BAIBA acted through the taurine transporter SLC6A6, downregulated PI3K/Akt/NF-κB signalling, and activated NRF2. In women with post-menopausal osteoporosis, serum L-BAIBA levels were lower and correlated with bone mineral density [17].

- **Muscle-bone crosstalk reviews** – Reviews on sarcopenia and osteoporosis emphasised that myokines such as BAIBA, myostatin, irisin, interleukin-6 and bone-derived factors like FGF23 and sclerostin mediate bone-muscle communication [18]. Postmenopausal osteoporosis reviews further highlighted BAIBA among cytokines that regulate both muscle and bone [19].

Human Bone Mineral Density and Physical Performance

- **Genetic loci and BAIBA (Transl Psychiatry 2023)** – A genome-wide association study identified variants in the AGXT2 gene associated with a metabolomic risk score for mild cognitive impairment and BAIBA levels. BAIBA mediated the association between these variants and mild cognitive impairment [20].

- **L-BAIBA and D-BAIBA with bone and performance (Sci Rep 2023)** – In a cohort of adults, plasma L-BAIBA was positively associated with body mass index and bone mineral density in females and with lean mass. D-BAIBA correlated with age and physical performance [21]. A related preprint reported similar associations [22].

- **Aminobutyric acids as osteoporosis biomarkers (Commun Biol 2020)** – As noted above, D-BAIBA and GABA correlated with physical activity and hip BMD [4], supporting BAIBA as a potential biomarker for bone health.

Clinical Studies and Human Associations

Cardiometabolic Health and Diabetes

- **SGLT2 inhibitors and BAIBA (Cardiovasc Diabetol 2022)** – Among 81 heart failure patients with type 2 diabetes, BAIBA was detected in 77 % of patients. Patients taking sodium-glucose co-transporter-2 (SGLT2) inhibitors had higher BAIBA detection rates (93 % vs. 67 %) and concentrations. Adjusted analyses showed SGLT2 inhibitor use was independently associated with elevated BAIBA, suggesting BAIBA may mediate some cardioprotective effects of these drugs [23].

- **Glucose metabolism in obesity (J Diabetes Res 2023)** – In obese adults, BAIBA concentrations did not differ between those with normal glucose tolerance and prediabetes. However, higher BAIBA was associated with higher adiponectin, a higher adiponectin/leptin ratio and lower glucose/insulin at 180 minutes during an oral glucose tolerance test [24]. Mediation analysis suggested adiponectin mediated the association between BAIBA and favourable glucose metabolism [24].

- **BAIBA, BCAA and body composition (J Nutr Sci 2016)** – Plasma branched-chain amino acids (BCAA) were higher in obesity and positively associated with visceral adiposity and insulin resistance. BAIBA did not correlate with BCAA but was negatively associated with subcutaneous fat and positively associated with insulin sensitivity [25]. This distinction underscores BAIBA's beneficial metabolic associations independent of BCAA.

- **Low-calorie diet raising BAIBA** – As discussed, caloric restriction in obese women increased BAIBA levels and improved metabolic parameters [9].

- **Antiretroviral drugs and fat wasting (Antivir Ther 2004)** – In mice, zidovudine, stavudine and BAIBA increased hepatic fatty-acid oxidation and ketone bodies, leading to decreased body fat without affecting food intake [26]. BAIBA mimicked the fat-wasting side effects of these nucleoside reverse transcriptase inhibitors, suggesting increased hepatic fat oxidation contributes to lipoatrophy.

Safety and Toxicity

- **Subchronic toxicity (Int J Toxicol 2022)** – L-BAIBA was administered orally to Sprague–Dawley rats at 100–900 mg/kg/day for 90 days. No adverse effects were observed, establishing a no-observed adverse effect level (NOAEL) of 900 mg/kg/day [27]. These findings support the safety of BAIBA supplementation.

- **Absorption kinetics (J Diet Suppl 2023)** – As noted, oral BAIBA doses up to 1500 mg in healthy adults increased plasma concentrations without side effects [5].

Neurological and Oxidative Stress Studies

- **Lung ischemia–reperfusion injury (Biomed Central 2023)** – BAIBA treatment in mice reduced lung edema, inflammation and neutrophil infiltration during ischemia–reperfusion injury. BAIBA activated the AMPK/Nrf-2 pathway and increased GPX4 and SLC7A11 expression. Blocking AMPK or Nrf-2 abrogated BAIBA's protective effect, indicating BAIBA prevents ferroptosis and tissue injury via the AMPK/Nrf-2/GPX4/SLC7A11 axis [28].

- **Type 1 diabetes-induced germ cell toxicity (Mutat Res 2024)** – In diabetic rats, BAIBA doses of 25–100 mg/kg improved hyperglycemia and body weight, reduced oxidative stress biomarkers, increased testosterone and FSH, improved sperm count/motility, decreased DNA damage and apoptosis and modulated the IGF-1/AMPK/SIRT-1 pathway [29]. These results suggest BAIBA may ameliorate diabetes-related reproductive toxicity.

- **Mild cognitive impairment (Transl Psychiatry 2023)** – The genome-wide association study mentioned earlier found that genetic variants influencing BAIBA levels were associated with mild cognitive impairment and that BAIBA mediated part of this association [20], hinting at a role for BAIBA in neurodegeneration.

- **BAIBA release and PC12 cells (IBRO Neurosci Rep 2021)** – BAIBA protected neuron-like cells from oxidative stress by activating AMPK and PI3K/Akt pathways [14].

Reviews and Broad Perspectives

- **Metabolic regulator and exercise pill (Front Endocrinol 2023)** – A comprehensive review summarised BAIBA as a metabolic regulator, biomarker and potential exercise pill. BAIBA is produced during valine and thymine catabolism and regulates lipid and glucose metabolism, inflammation, oxidative stress and bone health. The review noted that BAIBA produced during exercise has not shown side effects in humans or rodents [30].

- **Regulation of skeletal muscle by amino acids (Nutrients 2020)** – This review discussed how amino acids and their metabolites regulate skeletal muscle functions. BAIBA, derived from valine, is secreted from contracting muscle and acts on tissues such as white adipose to enhance energy expenditure [31].

Summary and Future Directions

Research over the past five decades has transformed BAIBA from a by-product of thymine metabolism into a multifunctional molecule with systemic effects. Early clinical studies established its link to thymine catabolism and cancer. Advances in analytical chemistry enabled separation of BAIBA enantiomers and quantification in human samples. The discovery of BAIBA as an exercise-induced myokine revealed roles in browning of white fat, hepatic fatty-acid oxidation, glucose homeostasis, osteocyte survival and osteoclast regulation. Human studies associate BAIBA with improved insulin sensitivity, bone mineral density and physical performance. Mechanistic studies demonstrate BAIBA acts through receptors such as MRGPRD and SLC6A6 and signalling pathways including AMPK, PI3K/Akt, PPARα and Nrf-2.

Clinical and safety studies show BAIBA levels rise with exercise, dieting and SGLT2 inhibitor therapy, and supplementation is well tolerated. However, BAIBA's dual origin (thymine vs. valine metabolism), distinct enantiomers and interactions with genetic variants such as AGXT2 require careful interpretation. Although BAIBA exhibits protective effects in cardiovascular, metabolic, bone and nervous systems, further trials are needed to evaluate its therapeutic potential, optimal dosing and long-term safety. Additionally, investigation into BAIBA derivatives (e.g., Oct-B), its role in neurodegenerative diseases and its utility as a biomarker for aging and metabolic health will deepen our understanding of this versatile metabolite.

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