3-2021

Health and ergogenic potential of oral adenosine-5'-triphosphate (ATP) supplementation

Ralf Jäger
Increnovo LLC

Martin Purpura
Increnovo LLC

John A. Rathmacher
MTI BioTech, Inc.

John C. Fuller Jr.
Metabolic Technologies, LLC

Lisa M. Pitchford
MTI BioTech, Inc.

See next page for additional authors

Journal of Functional Foods 78 (2021) 104357

Contents lists available at ScienceDirect

Journal of Functional Foods

journal homepage: www.elsevier.com/locate/jff

Health and ergogenic potential of oral adenosine-5′-triphosphate (ATP) supplementation

Ralf Jäger [a,*], Martin Purpura [a], John A. Rathmacher [b,c], John C. Fuller Jr. [d], Lisa M. Pitchford [b,e], Fabricio E. Rossi [f], Chad M. Kerksick [g]

[a] Increnovo LLC, 2138 E Lafayette Pl, Milwaukee, WI 53202, USA
[b] MTI BioTech, Inc., 2711 S. Loop Dr., Suite 4400, Ames, IA 50010, USA
[c] Dept. of Animal Science, Iowa State University, Ames, IA 50011, USA
[d] Metabolic Technologies, LLC, 135 W Main St, Suite B, Missoula, MT 59802, USA
[e] Dept. of Kinesiology, Iowa State University, Ames, IA 50010, USA
[f] Immunometabolism of Skeletal Muscle and Exercise Research Group, Department of Physical Education, Federal University of Piauí (UFPI), 64049-550 Teresina, Piauí, Brazil
[g] Exercise and Performance Nutrition Laboratory, School of Health Sciences, Lindenwood University, St. Charles, MO, USA

ARTICLE INFO

Keywords:
ATP
Exercise performance
Cardiovascular health

ABSTRACT

Adenosine triphosphate (ATP) is the primary compound that provides energy to drive many processes in living cells, including muscle contraction, neurotransmission, and cardiac function. Initial research used enteric-coated ATP that displayed no apparent efficacy. However, ATP disodium supplementation has demonstrated improved bioavailability and acute and chronic benefits to cardiovascular health, muscular performance, body composition, and recovery while attenuating muscle breakdown and fatigue. In this review, we provide a critical assessment of oral ATP's bioavailability and its various health and ergogenic benefits.

1. Introduction

1.1. ATP: Life's energy reservoir

Adenosine triphosphate (ATP) was first discovered in 1929 by the German chemist Karl Lohmann, who isolated ATP from muscle and liver extracts (Langen & Hucho, 2008). Found in every cell of the human body, ATP has been dubbed as the currency of energy affecting virtually every physiological process requiring energy. Energy, approximately 30.6 kJ/mole, is freed from the ATP molecule by a reaction that removes one phosphate group. The resulting adenosine diphosphate (ADP) is usually immediately recycled in the mitochondria where it is recharged again into ATP via phosphorylation (i.e., the adding of a phosphate group) (Fig. 1). Notably, each molecule of ATP in the human body will be recycled 2,000–3,000 times in a single day.

Beyond powering cellular processes, levels of and the presence (or absence) of intracellular ATP can communicate signals across cells once released into the extracellular space. Known as ATP signaling, and first detected between nerve cells and muscle tissue, ATP signaling occurs between a wide variety of cell types in the body (Khakh & Burnstock, 2009). While ATP's role in increasing skeletal muscle calcium permeability and other aspects of muscle contraction have been extensively studied (Burnstock & Kennedy, 1985; Burnstock, 2007), ATP signaling, due to the multiplicity of cell-surface ATP receptors found in a diverse array of tissues and cell types (Burnstock & Wood, 1996), plays a crucial role in a variety of biological processes including neurotransmission, blocking of chloride efflux, cardiac function, platelet function, vasodilatation and liver glycogen metabolism (Agteresch, Dagnelie, van den Berg, & Wilson, 1999; Khakh & Burnstock, 2009). Initial research using enteric-coated ATP questioned this formulation's bioavailability after oral administration. Recent studies, however, have demonstrated an increased potential for oral ATP supplementation when administered as ATP disodium. The purpose of this review was to summarize and assess the available literature base surrounding the oral administration of ATP relative to its bioavailability and health and physical performance outcomes.

2. Methods

While conducting this systematic review, the checklist and flowchart

* Corresponding author.
E-mail address: ralf.jaeger@increnovo.com (R. Jäger).

https://doi.org/10.1016/j.jff.2021.104357
Received 22 September 2020; Received in revised form 1 January 2021; Accepted 2 January 2021
Available online 20 January 2021

of Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) were used as a guide (Moher, Liberati, Tetzlaff, & Altman, 2009). The literature search process was performed in the PubMed, Scopus and Google Scholar literature databases. The MeSh terms were used and they included, "Adenosine-5'-triphosphate [Title] or ATP [Title] AND exercise [Title] or athlete [Title] or physical activity [Title]. In order to increase the accuracy of the selection of articles searched on Google Scholar, only articles that included related keywords were selected. All clinical trials that involved humans and articles published in the English language were included in this review. Articles excluded were studies that used in vitro models, animal studies, reviews, journals written in non-English language, and studies without access to full-text. From the studies that met eligibility criteria, extraction of data was done in which the author names, year of publication, study setting or location, study design, definite description and sample size, description of exposure, description of outcomes, description of the control group, the study findings, and covariates involving data processing were identified. Full-length article and data extraction were reviewed by two investigators independently. During the extraction process, the investigators discussed any discrepancies until they reached a mutual agreement. If needed, the corresponding authors of eligible articles were contacted for additional information. Fig. 2 provides a PRISMA flow diagram to illustrate these methods, and Table 1 is a summary table that addresses the major research design elements of the applicable literature.

3. Bioavailability

Continuous intravenous administration of ATP has been shown to significantly increase erythrocyte ATP pools by 40–60% (Rapaport, Salikhova, & Abraham, 2015). In addition, exogenously administered ATP rapidly degrades to adenosine while ATP levels accumulate inside erythrocytes. These changes suggest the presence of dynamic mechanisms that facilitate the uptake of adenosine from blood plasma. From here, ATP pools can then be released locally or globally from circulating erythrocytes.

ATP is rapidly dephosphorylated to ADP by hydrolysis in acidic environments such as that found in the stomach. The intraluminal pH changes rapidly from highly acidic (pH ~ 2.0) in the stomach to a pH of approximately 6.0 in the duodenum and then gradually increases to a pH of about 7.4 in the terminal ileum. ATP exhibits stability between pH 6.8 – 7.4 (Alberty, 1998), thus to protect ATP from the acidic environment in the stomach, enteric-coated oral ATP supplements were used in early absorption studies (Arts et al., 2012; Coolen et al., 2011; Jordan et al., 2004). However, oral administration of a single acute high-dose (5,000 mg) (Arts et al., 2012), 14 days of 150 or 225 mg per day (Jordan et al., 2004), and 28 days of 250, 1,250 or 5,000 mg per day (Coolen et al., 2011) of enteric-coated ATP all failed to significantly increase blood concentrations of ATP or its metabolites.

Later development realized that for effective duodenal absorption of ATP into the bloodstream, the enteric coating needs to dissolve at pH 5.5, the average pH of the proximal duodenum. Therefore, one potential explanation for the lack of change in ATP levels after oral administration of enteric-coated ATP could be the buffering capacity of ATP as disodium salt at pH 4.0–4.5 (Metzler, 1977). The enteric coating of the ATP disodium requires a pH of 5.5 for dissolution. The enteric coating might only partly dissolve and allow duodenal contents and water to penetrate in the moment of disintegration. As a result, the ATP disodium could keep the pH below 5.5, which would limit the extent to which dissolution occurs compromising its breakdown and subsequently its release of ATP disodium at the duodenum where it could be absorbed into the bloodstream.

Absorption of orally administered non-coated ATP (5 mg/kg/day ATP for 30 days) was tested in an animal model (Kichenin & Seman, 2000). In this study, improvements in adenosine uptake, ATP synthesis, and ATP exportation by red cells were found to occur. Using a human infusion model, Rapaport and investigators infused ATP into advanced malignancy cancer patients for eight hours over eight weeks (Rapaport et al., 2015). These authors posited that ATP itself does not transport across plasma membranes and is first broken down to adenosine. From there adenosine is then taken up by erythrocytes and subsequently expands the total erythrocyte ATP pool. These data suggest that, despite its expected gastric instability, oral ATP supplementation may not require an enteric coating to exert beneficial physiological effects. Subsequently, Purpura et al., 2017 used a human investigation involving oral uncoated ATP disodium supplementation for 15 days at a dose of 400 mg per day. While adenosine was not measured in this investigation,

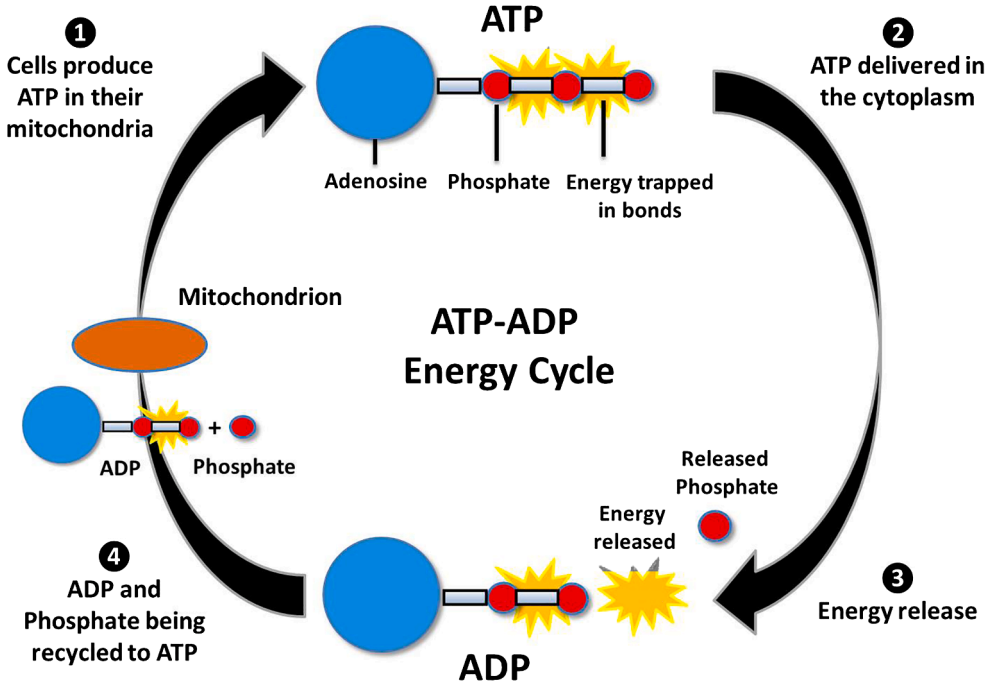

Fig. 1. Energy is freed from ATP by removing one of the phosphate groups yielding ADP. ADP is then recharged into ATP via phosphorylation.

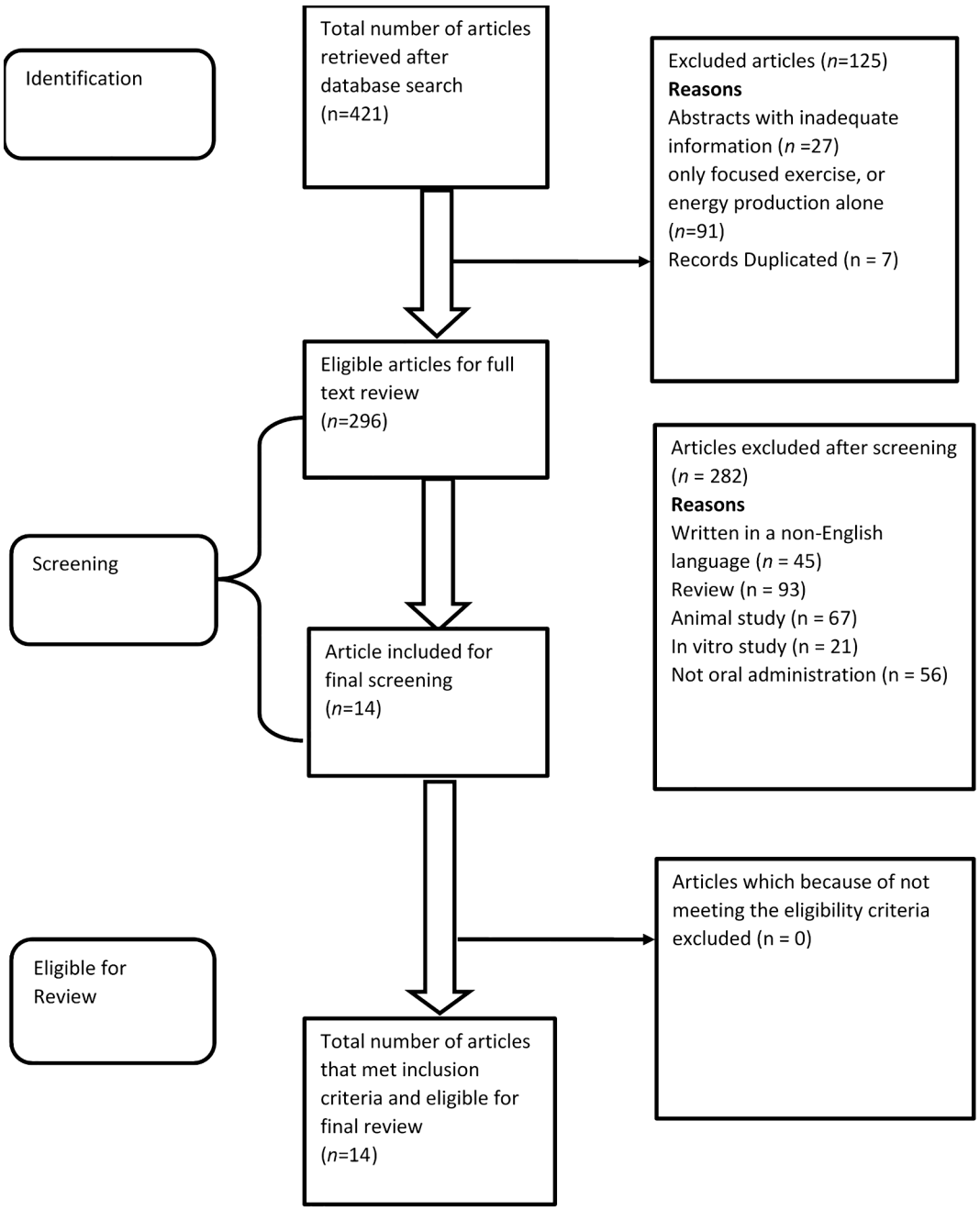

Fig. 2. Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for selection of eligible articles.

supplementation was found to prevent decreases in ATP, ADP, and AMP in the blood 30 min following high-intensity exercise in comparison to the placebo (Purpura et al., 2017) (Fig. 3).

These findings are important as prior investigations only examined resting conditions and failed to identify any significant increases in ATP levels (Arts et al., 2012; Coolen et al., 2011; Jordan et al., 2004). It is, therefore, hypothesized that an indirect mechanism for ATP re-synthesis exists, whereby the chronic ingestion of oral non-enteric coated ATP disodium increases the capacity of erythrocytes or other cellular components or structures to synthesize and better sustain plasma ATP concentrations in response to the hypoxic perturbations, such as those triggered by high-intensity exercise. It is further proposed that ATP and/or its respective metabolites (i.e., ADP and AMP) may stimulate intracellular ATP synthesis via reactions similar to the myokinase reaction or by interacting with specific ATP and adenosine receptors on the cells surface through a signalling effect (Freitas et al., 2019). As such, several open questions remain regarding the potential or actual operative functions which outline the observed bioavailability of oral ATP supplementation, and more research is needed to better understand the physiological and biochemical implications of these mechanisms with and without external hypoxic triggers such as intense physical exercise.

4. Effects of ATP supplementation on muscular performance and body composition

It is hypothesized that the improvement in ATP turnover (e.g., prevention of ATP decline or improvement in ATP:ADP ratio) through oral supplementation of ATP could allow athletes to maintain performance through longer periods of exertion and consequently delay the onset of fatigue. Theoretically, this heightened performance would allow for a

Table 1
Summary table of studies examining outcomes related to ATP administration. Studies are first grouped into absorption, sports, and then non-sports studies. Individual references are sorted alphabetically within each group within the table.

Study	Design	Subjects	Methods	Supplementation	Duration	Main Findings (Effect of ATP)
Absorption Studies						
Arts et al. (2012)	Randomized, placebo-controlled, cross-over	8 healthy men (2) and women (6) (age = 27 ± 6 yrs)	Blood sampling	5000 mg ATP disodium as proximal-release and distal-release pellets	1 Week	No effect on blood ATP concentrations.
Coolen et al. (2011)	Randomized, double-blind, placebo-controlled	32 healthy men (29 ± 14 yrs)	Blood sampling	0, 250, 1250 or 5000 mg ATP disodium. In addition, 5000 mg dose on days 0 and day 28.	4 Weeks	All patterns of ATP supplementation for 4 weeks did not lead to changes in blood or plasma ATP concentrations, only resulted in increased uric acid concentrations.
Jordan et al. (2004)	Randomized, double-blind, placebo-controlled	27 men (high dose ATP N = 9, 29 ± 8 yrs; Low Dose ATP N = 9, 30 ± 7 yrs; placebo N = 9, 29 ± 6 yrs)	Blood sampling	150 mg or 225 mg of enteric coated ATP disodium	14 Days	Acute supplementation non-significantly increased total blood ATP levels (225 mg: +11%; 150 mg: +10%), chronic supplementation had no effect on whole blood ATP, or plasma ATP concentrations.
Purpura et al. (2017)	Randomized, double-blind, placebo-controlled	42 resistance trained men (ATP N = 21, Placebo N = 21, age = 20 ± 3 yrs)	Blood sampling	400 mg ATP disodium for 14 days	15 Days	No effect on resting ATP levels, but prevented exercise-induced declines in ATP and ADP levels ($p < 0.05$).
Sports Studies						
Freitas et al. (2019)	Randomized, double-blind, placebo-controlled, cross-over	11 recreationally resistance trained men (28 ± 6 yrs)	Lower body resistance exercise	400 mg ATP disodium; 30 min pre-exercise	Single dose	Significantly improved athletic performance: higher total weight lifted ($p = 0.05$). Significantly greater oxygen consumption during exercise ($p = 0.021$).
Jäger et al. (2014)	Pilot study	12 resistance-trained men (age = 24 ± 4 yrs)	Acute arm exercise	400 mg ATP disodium 30 min pre-breakfast	12 Weeks	Significantly increased blood flow and brachial dilation at weeks 1, 8, and 12 ($p < 0.05$).
Jordan et al. (2004)	Randomized, double-blind, placebo-controlled	27 men (high dose ATP N = 9, 29 ± 8 yrs; Low Dose ATP N = 9, 30 ± 7 yrs; placebo N = 9, 29 ± 6 yrs)	Anaerobic exercise performance	150 mg or 225 mg of enteric coated ATP disodium	14 Days	At 225 mg dose, increased 1RM, repetitions to fatigue, and total lifting volume at post-test
Purpura et al. (2017)	Randomized, double-blind, placebo-controlled	42 resistance trained men (ATP N = 21, Placebo N = 21, 20 ± 3 yrs)	Sprint protocol	400 mg ATP disodium before breakfast; on day 15, 30 min pre-exercise	15 Days	Significantly increased Wingate peak power in later bouts compared to baseline. Prevented the decline in muscle excitability in later bouts ($p < 0.0001$).
Rathmacher et al. (2012)	Randomized, double-blind, placebo-controlled, cross-over	16 recreationally active men (N = 8) and women (N = 8) (25 ± 3.9 yrs)	Strength and fatigue testing	2 × 200 mg ATP disodium; pre-breakfast/dinner	15 Days	Improved leg muscle low peak torque in set 2 ($p < 0.01$); tended to decrease leg muscle fatigue in set 3 ($p < 0.10$).
Wilson et al. (2013)	Randomized, double-blind, placebo- and diet-controlled	21 resistance-trained men (ATP N = 11, Placebo N = 10, age = 23 ± 1 yrs)	Phase 1 - periodized resistance-training, Phase 2 - overreaching cycle, Phase 3 - two-week taper	400 mg ATP disodium on non-training days pre-breakfast or 30 min pre-exercise	12 Weeks	Significantly increased lean body mass ($p < 0.001$) and muscle thickness ($p < 0.02$) over training alone. Significantly increased total strength and vertical jump power ($p < 0.001$).
Non-Sports Studies						
Bannwarth et al. (2005)	Randomized, double-blind, parallel-group, placebo-controlled	162 men and women (ATP N = 81, 43 ± 10 yrs; placebo N = 80 41 ± 10 yrs) with a diagnosis of subacute lower back pain.	One-month therapy	90 mg ATP disodium	One Month	Significantly improved RDQ at day 7 ($p = 0.02$). Significantly less use of rescue analgesic.
de Freitas et al. (2018)	Randomized, double-blind, placebo-controlled, cross-over	11 hypertensive women (62 ± 5 yrs)	Walking exercise	400 mg ATP disodium; 30 min pre-exercise	Single dose	Faster recovery of heart rate variability; reduced systolic blood pressure after exercise ($p < 0.05$).
Hirsch et al. (2017)	Randomized, double-blind, placebo-controlled	53 subjects (23 men, 30 women; 55 ± 6 yrs)	Weight loss parameters and flow mediated dilation	200 mg ATP disodium, 200 mg ATP disodium plus 1,000 mg GlycoCarn, 1,000 mg GlycoCarn	90 Days	Significantly decreased in blood glucose, malondialdehyde levels, waist and hip circumference, and waist/height ratio; significantly increased flow-mediated dilation ($p \leq 0.05$).
Ju et al. (2016)	Case study	7-year-old boy with ATP1A3 mutation, presenting with recurrent hemiplegic episodes	2 Year therapy	20-to100 mg ATP disodium twice a day; gradually increased	2 Years	Significantly lower frequency and shorter duration of hemiplegic episodes. Marked amelioration of alternating hemiplegia of childhood episodes, and

(*continued on next page*)

Table 1 (*continued*)

Study	Design	Subjects	Methods	Supplementation	Duration	Main Findings (Effect of ATP)
						improved psychomotor development.
Long and Zhang (2014)	Randomized, double-blind, placebo-controlled	244 total knee replacement patients (ATP N = 119, 60 ± 5 yrs; placebo N = 113, 59 ± 5 yrs)	4 Weeks therapy	120 mg ATP disodium three times a day	4 Weeks	Significantly improved quadriceps strength and pain scores at postoperative days 7, 14, 21, and 28 ($p \leq 0.05$). Decreased need for analgesics by 5% and shortened the length of hospital stay by 12%.
Rossignol et al. (2005)	Double-blind (only trial 1), randomized placebo-controlled	Trial 1 (ATP N = 80, 41 ± 10 yrs; placebo N = 80, 43 ± 10 yrs); Trial 2 (ATP N = 81, 41 ± 11 yrs; without ATP N = 76, 44 ± 10 yrs)	30 Days therapy	90 mg ATP disodium	90 days ± 5 days	Improved RDQ ($p = 0.02$). ATP group patients were three times less likely to report a condition that had worsened or remained unimproved at 90 days ($p = 0.02$).

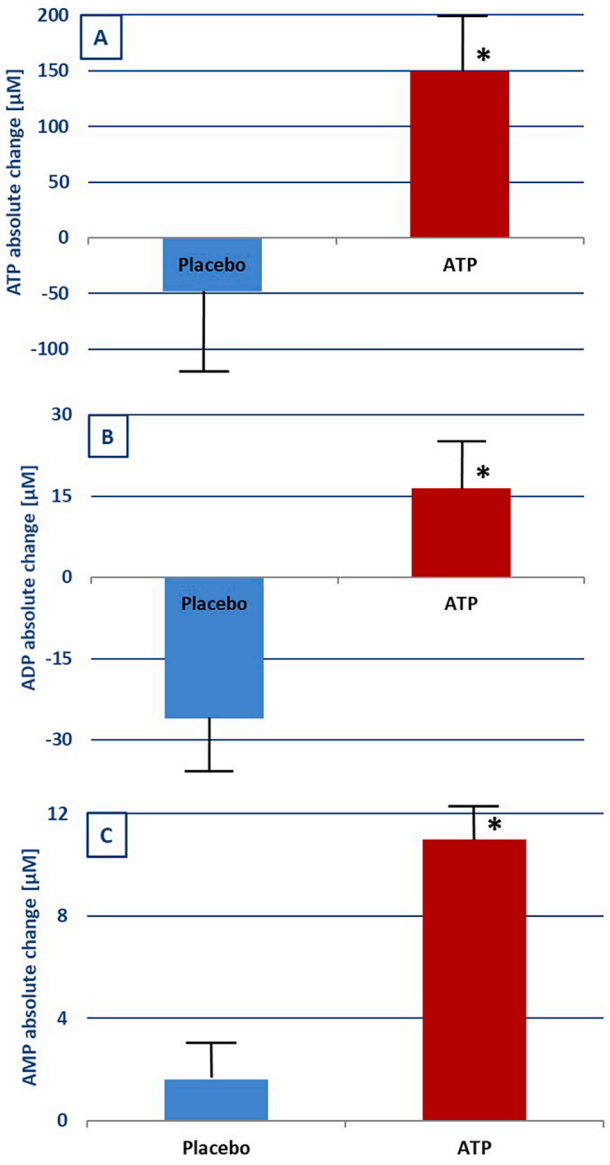

Fig. 3. Delta changes in blood ATP (A), ADP (B), and AMP (C) levels from pre-exercise to 30 min post-Wingate exercise in participants supplemented with ATP disodium or a placebo for 15 days (*$p < 0.05$ different from placebo group) (Purpura et al., 2017).

greater completion of work, which sets the stage for greater exercise training adaptations. These potential benefits of ATP disodium supplementation were investigated in a series of clinical studies (Freitas et al., 2019; Jordan et al., 2004; Purpura et al., 2017; Rathmacher et al., 2012; Wilson et al., 2013).

Jordan et al. published one of the first investigations to examine the acute impact of two different doses (150 and 225 mg) of non-enteric coated ATP (Jordan et al., 2004). Twenty-seven healthy, previously active males were supplemented in a randomized, double-blind fashion to either a placebo, 150 mg, or 225 mg doses of ATP for a period of 14 days. After 7 and 14 days of supplementation, participants completed two Wingate tests and three sets of maximal bench press repetitions with 70% of a pre-determined one-repetition maximum (1RM). Results from this study showed that 225 mg of enteric-coated ATP significantly increased the number of repetitions to fatigue during the first of three sets of bench press repetitions (+18.5%, $p < 0.007$) as well as total lifting volume (+22%, $p < 0.003$) in comparison to baseline. These changes, however, were not statistically different than the non-significant improvements also observed in the placebo and low dose group (150 mg enteric-coated ATP) for repetitions completed and total lifting volume. No changes were observed in sets 2 or 3 of completed bench press repetitions nor any anaerobic power metrics collected during the Wingate tests. No within or between-group differences were observed for lactate or blood ATP concentrations. Results from this study are challenging to reconcile as the authors used an enteric-coated ATP formulation and a lower dose than most other investigations (225 mg vs. 400 mg). Further, from a timing perspective, the authors administered the supplements three hours before testing versus the more typical 30-min window and as such, timing of ATP administration may be another factor to consider when evaluating these results.

Freitas and investigators examined the impact of a single 400 mg dose of non-enteric coated ATP in a randomized, double-blind, crossover study design in 11 healthy, previously active males (Freitas et al., 2019). Thirty minutes after ingestion, participants completed a series of half-squat repetitions with 80% of their 1RM. Performance was recorded as total repetitions completed, and oxygen consumption, lactate and hemodynamic parameters were also assessed. In comparison to placebo, the total weight lifted was significantly increased (Placebo: 3995.7 ± 1137.8 vs. ATP: 4967.4 ± 1497.9 kg, $p = 0.005$) when the ATP dose was provided. Significant group effects were found whereby heart rates were higher after the 4th set ($p < 0.001$) and oxygen consumption ($p = 0.021$) was higher in ATP when compared to placebo. No differences between conditions were found for lactate or blood pressure (Fig. 4).

The impact of ATP supplementation on repeated bouts of maximal exercise performance was investigated by Purpura et al. using a randomized, double-blind, placebo-controlled approach (Purpura et al., 2017). Healthy males (n = 42) completed a 14-day supplementation protocol of 400 mg/day and on the 15th day took their prescribed dose 30 min before completing ten repeated 6-second cycling sprints with

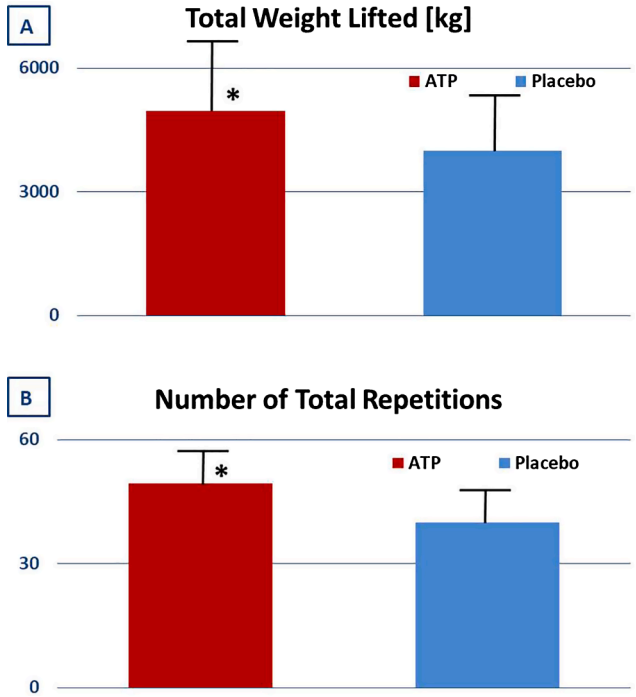

Fig. 4. Acute ATP supplementation significantly increased training volume and number of repetitions (*$p < 0.05$ different from placebo group) (Freitas et al., 2019).

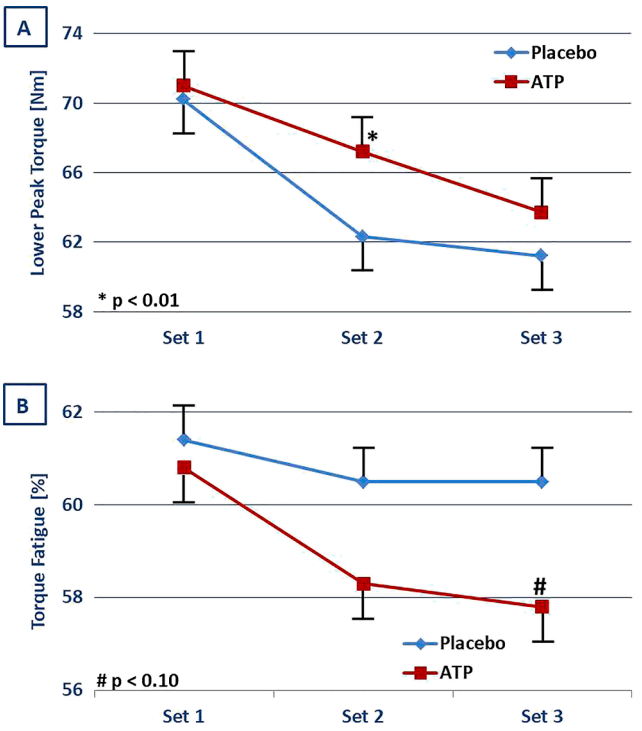

Fig. 5. ATP supplementation improved peak torque (A) and reduced fatigue in later sets of 50 maximal knee extensions (B) (*$p < 0.05$ and $^{\#}p < 0.1$, different from placebo group) adopted from Rathmacher et al. (2012).

30 s of rest between each sprint. As expected, maximal power output decreased in both groups, but performance was better maintained during the latter bouts (8th bout [Mean difference: 102.6 W; 95% CI: 21.6–183.5 W] and 10th bout [Mean difference: 90.8 W; 95% CI: 9.8–171.8 W]) when ATP was provided. Moreover, effect sizes were calculated for each of the ten sprint cycling bouts before and after supplementation. The average effect sizes (d) were 0.128 (range: $d = -0.01$ to 0.29) and 0.314 (range: $d = -0.18$ to 0.79) for the placebo group and ATP supplemented groups, respectively. No impact was reported for vertical jump power, reaction time, or muscle activation; however, muscle excitability increased significantly in the ATP group (+21.5%, $p < 0.02$) after bout 2 and helped to prevent the decline observed in the placebo group. While more research is needed, the lack of observed change for some outcomes (vertical jump) and not others (maximal power output) could be explained by the bioenergetic demand initiated by the repeated bouts of exercise. In an additional study that examined the impact of ATP supplementation on fatigue prevention, Rathmacher et al. had participants complete three sets of 50 maximal knee extensions to induce fatigue after supplementing with ATP (two doses of 200 mg/day) or placebo using a randomized, double-blind, placebo-controlled, crossover design (Rathmacher et al., 2012). No differences were detected in high peak torque, power, or total work with ATP supplementation. ATP supplementation did, however, improve low peak torque in set number two (ATP: 67.2 N-m vs. placebo: 62.3 N-m, $p < 0.01$), and torque fatigue tended to be improved with ATP (ATP: 57.8% vs. placebo: 60.5%, $p < 0.10$) in the third set of maximal repetitions (Fig. 5). Two key discussion points arise from this study. First, results from this study provide additional evidence that ATP supplementation may lack the ability to exert ergogenic outcomes during the early phases of an intense bout of exercise, but it does seem to enhance resistance to the accumulation of fatigue that inevitably results from maximal muscular contractions. Second, this study used a split dose (2×200 mg) supplementation protocol and, it is important to note, participants did not supplement on the day of the testing, missing out on the potential acute benefits of ATP supplementation.

Wilson and colleagues had 21 resistance-trained males supplement with either 400 mg/day of ATP or placebo in a randomized, double-blind, placebo-controlled fashion in conjunction with a 12-week heavy resistance training program (Wilson et al., 2013). The 12-week protocol consisted of an eight week periodized resistance-training program, two weeks of an overreaching cycle, and two weeks of tapering. Using this approach, ATP supplementation led to significantly greater improvements in muscle thickness (as determined by ultrasound) and maximal strength and vertical jump power (Wilson et al., 2013). Specifically, the ATP group experienced significant increases in squat 1RM ($p < 0.001$) and deadlift 1RM ($p < 0.001$) resulting in significantly greater improvements in total strength (PLA: +5.9% [22.4 ± 7.1 kg] vs. ATP: +12.6% [55.3 ± 6.0 kg], $p < 0.001$). Additionally, significantly greater improvements in vertical jump power were found for ATP supplementation (PLA: +11.6% [614 ± 52 W] vs. ATP: 15.7% [796 ± 75 W], $p < 0.001$). Interestingly, no changes were observed for bench press 1RM ($p = 0.65$) or Wingate peak power ($p = 0.48$). The discordance of observed change in upper-body strength and lower-body strength is somewhat surprising; however, the amount of musculature involved may be a key consideration as previous work involving caffeine and acute resistance training performance has resulted in a similar pattern of outcomes. Additionally, no change was observed in Wingate peak power ($p = 0.48$) between PLA and ATP supplemented individuals. While both outcomes are intended to assess a representation of power, the time and relative energetic demand between a vertical jump and Wingate anaerobic capacity test are noticeably different and the role of ATP in energy homeostasis can seemingly operate as a key difference in these outcomes and their associated findings from this study. Wilson et al. also assessed changes in body composition. Lean mass gains occurred in both groups, but changes were found to be significantly greater in the ATP supplemented group (PLA: +2.92% [~2 kg increase] vs. ATP: +5.91% [~4 kg increase], $p < 0.009$) (Wilson et al., 2013). Similarly, muscle thickness levels were found to also increase to a greater extent in the ATP group (PLA: +4.9% [2.5 ± 0.6 mm] vs. ATP: +9.4% [4.9 ± 1.0 mm], $p < 0.02$). (Fig. 6). Notably, the improvements in body

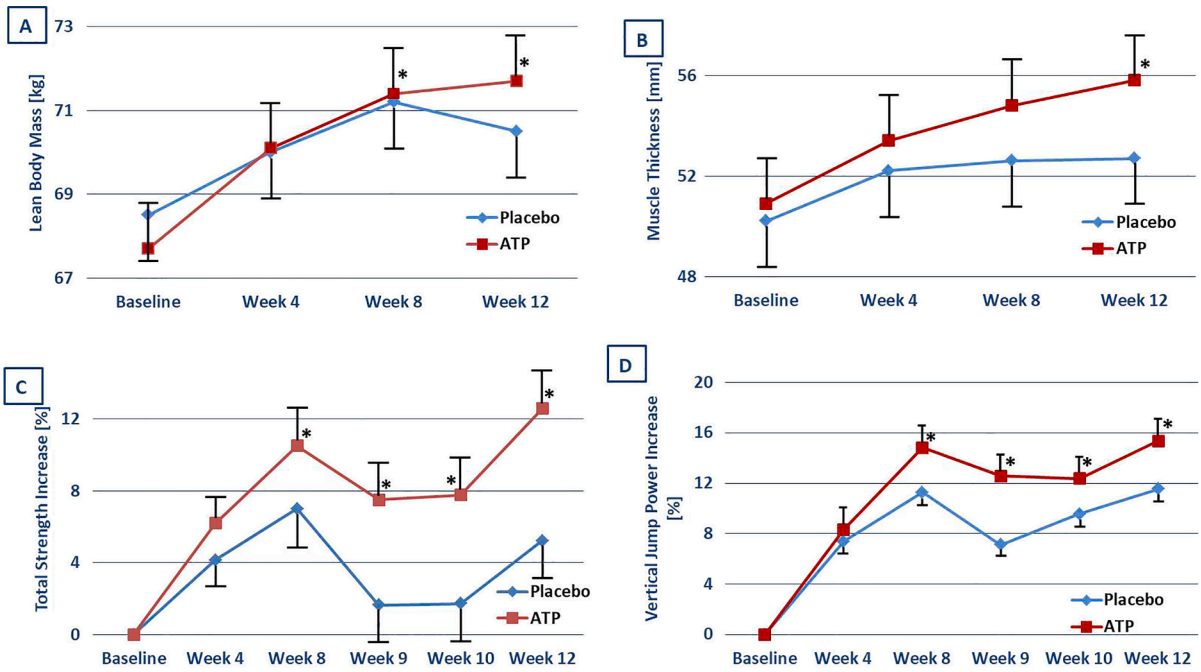

Fig. 6. ATP supplementation significantly increased lean body mass (A), muscle thickness (B), strength (C), and power (D) during a multi-week, controlled resistance training program (*$p < 0.05$ different from placebo group) (16). Adapted from Wilson et al. (Wilson et al., 2013).

composition in resistance-trained males over 12 weeks align with earlier findings that 90 days of ATP supplementation in a healthy, older (~55 years) population improved waist (-3.05 cm, $p = 0.04$) and hip circumference (-3.05 cm, $p = 0.007$), and waist-hip ratio (-0.02, $p = 0.03$), independent of any exercise or physical activity intervention (Hirsch et al., 2017).

5. ATP supplementation and recovery

Unaccustomed exercise stress or high volumes of exercise are common circumstances for physically active individuals and can result in brief periods of overreaching, a period where the body is too stressed to adequately recover. Twelve weeks of oral supplementation with ATP (400 mg/day) in young, resistance-trained males has been shown to attenuate losses of strength and power during a two-week overreaching period (Wilson et al., 2013). Total strength (sum of squat, bench press, deadlift 1RM) decreased in the control group (−5.0%, −22.6 ± 5.1 kg) whereby total strength loss was significantly attenuated in the ATP supplemented group (−2.2%, 12.0 ± 2.5 kg, $p < 0.007$). Moreover, the two-week overreaching protocol led to a 5.0% decrease in vertical jump power in the PLA group, whereas a significantly smaller decline (only 2.2%) was observed in the ATP group ($p < 0.001$) (Fig. 7).

Outcomes reported by Long et al. on performance and clinical outcomes in 232 patients who underwent total knee arthroplasty indicated greater recovery of force production in ATP supplemented individuals 7 (92.8 vs. 82.9 N), 14 (119.3 vs. 105.2 N), 21 (130.8 vs. 121.2 N), and 28 (190.2 vs. 175.3 N) days after surgery (all $p < 0.05$ between groups) as well as decreases in reported pain levels 7 (3.05 vs. 3.68), 14 (2.58 vs. 2.96), 21 (2.10 vs. 2.48), and 28 (1.56 vs. 1.98) days after surgery (in all instances data is presented as ATP vs. PLA, $p < 0.05$ between groups) (Fig. 8, Long & Zhang, 2014). However, no differences were observed between groups in either outcome at one or three days after surgery. These outcomes are intriguing, as they suggest that, while a measurable benefit of ATP supplementation in recovery from surgery may not be realized until at least day three of supplementation, the benefits may extend beyond 28 days of supplementation. Additional studies have highlighted the potential for ATP administration to impact medical recovery and to have implications related to pain. For example, ATP

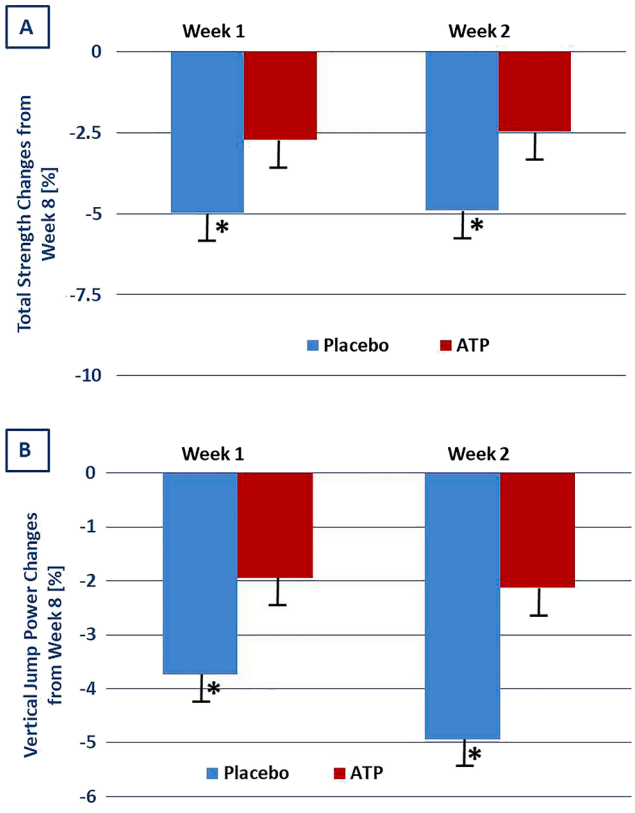

Fig. 7. ATP supplementation reduces losses of strength (A) and power (B) during an overreaching cycle (*$p < 0.05$ different from placebo group) (Wilson et al., 2013).

supplementation significantly shortened the length of hospital stay by 12% (PLA: 2.5 ± 0.7 days vs. ATP: 2.2 ± 0.8 days, $p = 0.003$) and reduced the need for rescue pain medication by 5% (PLA:

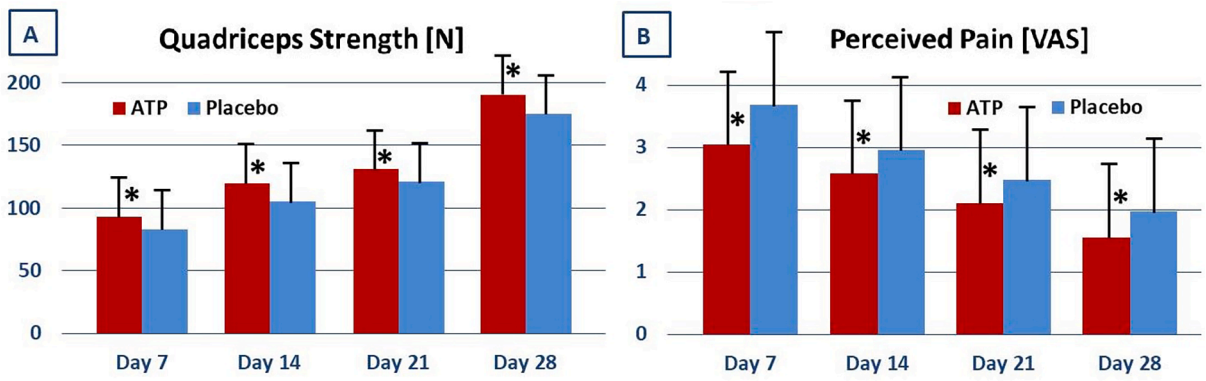

Fig. 8. ATP supplementation decreases losses in strength (A) and improved perceived pain (B) following total knee replacement surgery (*$p < 0.05$ different from placebo group) (Long & Zhang, 2014).

1300 ± 202 mg vs. ATP: 1235 ± 185 mg, $p = 0.012$) (Long & Zhang, 2014). Two other studies, one by Moriyama et al. (2004) and another by Hayashida et al. (2005) both indicated positive potential for ATP infusion in terms of pain management. The Moriyama study infused ATP (dosage of 1 mg /kg) or a glucose control once per week for 12 weeks in eight patients with postherpetic neuralgia and found improvements in continuous and paroxysmal pain. Additionally, the Hayashida et al. study infused 12 postherpetic neuralgia with either ketamine, lidocaine, or ATP and found that ATP responders developed significant pain relief over a nine-hour period of time.

The potential for ATP to favorably impact recovery of lost strength and power after overtraining or surgical intervention points to some interaction of ATP availability with skeletal muscle health. Rates of muscle protein breakdown are increased during injury, inactivity (muscle disuse atrophy), energy restriction, and as a normal process of aging (age-related muscle loss or sarcopenia) (Tipton, Hamilton, & Gallagher, 2018). Wilson and investigators (Wilson et al., 2013) collected 24-hour urine samples from healthy, resistance-trained males who supplemented with 400 mg/day of ATP or placebo in a randomized, double-blind fashion to assess changes in urinary 3-methyl-histidine, a marker of myofibrillar protein breakdown. ATP supplementation was found to significantly ($p < 0.007$) prevent (Week 8: 0.143 ± 0.007 vs. Week 10: 0.131 ± 0.012 μmol/mg) the 23.7 ± 4.5% increase in level of urinary 3-methyl-histidine observed in the placebo group (Week 8: 0.123 ± 0.004 vs. Week 10: 0.152 ± 0.005 μmol/mg, (Fig. 9). ATP supplementation did not appear to have an impact, however, over changes in C-reactive protein ($p = 0.99$), cortisol ($p = 0.86$), free testosterone ($p = 0.93$), total testosterone ($p = 0.83$), creatine kinase ($p = 0.91$) or perceived recovery score ($p = 0.61$).

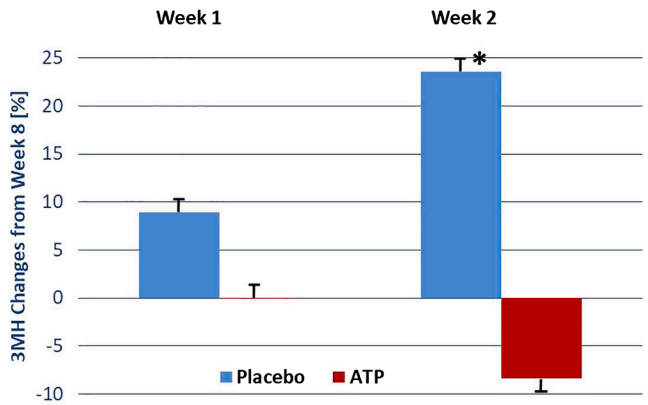

Fig. 9. ATP supplementation decreases urinary levels of 3-methyl-hisitidine (3MH), a marker of myofibrillar protein breakdown during an overreaching cycle (*$p < 0.05$ different from placebo group) (Wilson et al., 2013).

6. Health and clinical applications of ATP supplementation

ATP has varying effects within the cardiovascular system, including constriction, dilation, and the repair of blood vessels (Khakh & Burnstock, 2009). If an endothelial cell is damaged at a wound site, it spills ATP which breaks down to ADP. ADP then binds to receptors on platelets, which respond by aggregating to form a blood clot that closes the wound (Khakh & Burnstock, 2009). Moreover, changes in blood flow produce "shear stress" on endothelial cells lining blood vessel walls, causing the endothelial cells to release ATP, which activates receptors on nearby endothelial cells that respond by releasing nitric oxide, which makes the vessels relax (Khakh & Burnstock, 2009). Potential implications of ATP supplementation on vascular health have been studied using flow-mediated dilation (FMD), which measures the ability of an artery to dilate in response to a shear stress stimulus. In a pilot study, twelve healthy, resistance-trained males were supplemented for 12 weeks with 400 mg/day of ATP supplementation. No placebo was administered in the pilot trial. After 0, 1, 4, 8, and 12 weeks of supplementation, blood flow changes in the brachial artery were assessed using flow-mediated dilation in conjunction with an acute upper-arm exercise protocol (Jäger et al., 2014). Blood flow and brachial artery diameter significantly increased when ATP supplementation was provided, but the lack of control group in this study compromises the ability to more fully understand the potential of ATP to impact blood flow (Fig. 10). In addition, acute and long-term benefits of ATP supplementation on cardiovascular health in non-athletic populations have been reported (de Freitas et al., 2018). In 11 hypertensive older women (61.8 ± 5.0 years), a randomized, double-blind, placebo-controlled trial with a single

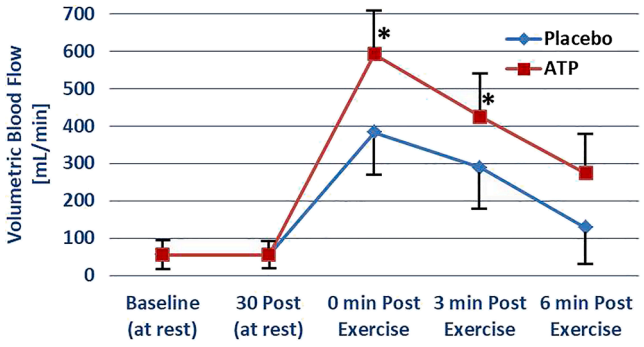

Fig. 10. Release of ATP activates receptors on endothelial cells which respond by releasing nitric oxide, inducing improved blood flow (A). ATP supplementation alone did not increase blood flow, but ATP did significantly enhance the post-exercise increase in blood flow (B), as measured by ultrasonography of the brachial artery. (*$p < 0.05$ different from placebo group) (19). Adapted from Jäger et al. (2014).

400 mg ATP disodium dose induced faster recovery of heart rate variability and reduced systolic blood pressure after 30 min of aerobic exercise. Hirsh et al. completed a randomized, double-blind, placebo-controlled investigation in 53 overweight and obese elderly men and women over a 90-day protocol of 100 mg/day, 2x/day of ATP supplementation (Hirsch et al., 2017). While no statistically significant changes were observed in comparison to the changes observed in the placebo group, the ATP group experienced significant increases (from its respective baseline) in blood flow (2.8%, $p = 0.003$) and malondialdehyde (0.92 μM, $p = 0.02$) and decreases in blood glucose (−6.3 mg/dL, $p = 0.02$), waist circumference (−3.05 cm, $p = 0.04$), hip circumference (−3.05 cm, $p = 0.007$), waist-to-hip ratio (−0.02, $p = 0.03$).

Finally, several clinical applications of ATP and adenosine have been reported (Agteresch et al., 1999). Oral ATP supplementation at a dosage of 90 mg/day significantly reduced participant's self-assessment of their disability levels and reduced the usage of rescue analgesics in 181 men and women with category 1 or 2 subacute lower back pain (Bannwarth et al., 2005). In a separate publication from the same research group, patients who supplemented with ATP were three times less likely to report a condition that had worsened or remained unimproved and took fewer rescue drugs (Rossignol et al., 2005). Finally, in a pediatric case study of a child with alternating hemiplegia, an intractable neurological disorder, reported that oral ATP supplementation reduced both the frequency and duration of hemiplegic episodes (Ju et al., 2016). While the results of these early studies are promising, additional studies on oral ATP supplementation in clinical conditions are warranted.

7. Future perspectives

Currently, ATP disodium has demonstrated the potential to impact several physiologic effects which may confer acute to long-term benefits on exercise performance and health. While preliminary bioavailability research has been completed, more research is needed to fully understand the kinetics and specifics of how the ingested molecules are transported through the digestive system and deposited in the circulation. Thus, immediate research efforts should focus on elucidation of the mechanism responsible for the observed outcomes in the literature. Future studies should investigate the potential ability of acute ATP disodium supplementation to impact various types of exercise performance and evaluate if there is a dose-dependent effect. As the knowledge base surrounding ATP supplementation and exercise performance matures, the next wave of research should investigate the potential for additive or even synergistic effects of co-administering ATP with other nutritional supplements that possess different or similar mechanisms-of-action. As an example, co-administration of ATP with beta-hydroxy-beta-methylbutyrate (HMB) has previously been shown to result in significant improvements in resistance training adaptations observed in resistance-trained males who followed a resistance training and supplemented with a combination of HMB and ATP for a period of 12 weeks (Lowery et al., 2016). Results of this study have been criticized for discrepancies in how the data was reported and methodological approaches used (Phillips et al., 2017), thus more follow-up work should be completed with this and other potential combinations of candidate nutrients. Of interest are supplements known to demonstrate buffering capacity in the body (i.e., creatine, beta-alanine, and bicarbonate) which could potentiate the half-life of ATP either in the gut or possibly the blood when co-administered.

Future research should also ascertain if these physiological mechanisms may differ between populations, such as in young vs. old, men vs. women, and untrained vs. trained individuals. In reference to aging, significant interest exists involving the role and impact of mitochondrial health as it relates to the aging process and longevity (Vendelbo & Nair, 2011). While the relationship between mitochondrial health and aging has been found in some but not all studies, a relationship between ATP production and aging has been observed in some studies and subsequently deserves more detailed investigation into its potential. Moreover, clinical populations such as individuals with chronic obstructive pulmonary disease or intermittent claudication are both characterized by peripheral muscle weakness that can limit exercise capacity resulting in a reduction in quality of life in these patients. As such, supplementation of ATP disodium could be an important strategy to improve oxygen delivery or utilization by the peripheral muscles and improve quality of life in these people.

8. Conclusion

The available literature on ATP disodium when provided in a dose of at least 400 mg approximately 30 min before a workout or 20–30 min before breakfast on non-exercise days provides insight into its potential to reduce fatigue (Purpura et al., 2017; Rathmacher et al., 2012), increase strength and power (Wilson et al., 2013), improve body composition (Hirsch et al., 2017; Wilson et al., 2013), maintain muscle health during stress (Long & Zhang, 2014; Wilson et al., 2013), increase recovery and reduce pain (de Freitas et al., 2018; Khakh & Burnstock, 2009; Wilson et al., 2013). Additionally, other literature indicates a role for ATP in improving cardiovascular health (Hirsch et al., 2017; Ju et al., 2016; Rossignol et al., 2005). The divergent findings surrounding ATP supplementation and an unidentified mechanism of action continue to preclude stronger conclusions from being made at this time. Therefore, additional research is needed to identify and clarify the cellular mechanism responsible for the observed changes as well as to replicate the findings already published in the literature.

9. Ethics statement

This manuscript is a review article and did not include any human subjects and animal experiments.

Author contribution

RJ and MP took the lead in writing the manuscript. All authors discussed the results and contributed to the final manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JCF is an employee of Metabolic Technologies, LLC an affiliate of TSI USA LLC, the manufacturer of Peak ATP. JAR and LMP are employees of MTI BioTech, Inc. which has a partnership with TSI USA, LLC. RJ and MP are consultants to TSI USA, LLC. All other authors do not declare competing interests.

References

Agteresch, H. J., Dagnelie, P. C., van den Berg, J. W., & Wilson, J. H. (1999). Adenosine triphosphate: Established and potential clinical applications. *Drugs, 58*(2), 211–232. https://doi.org/10.2165/00003495-199958020-00002.

Alberty, R. A. (1998). Change in the binding of hydrogen ions and magnesium ions in the hydrolysis of ATP. *Biophysical Chemistry, 70*(2), 109–119. https://doi.org/10.1016/s0301-4622(97)00114-2.

Arts, I. C., Coolen, E. J., Bours, M. J., Huyghebaert, N., Stuart, M. A., Bast, A., & Dagnelie, P. C. (2012). Adenosine 5'-triphosphate (ATP) supplements are not orally bioavailable: A randomized, placebo-controlled cross-over trial in healthy humans. *Journal of the International Society of Sports Nutrition, 9*(1), 16. https://doi.org/10.1186/1550-2783-9-16.

Bannwarth, B., Allaert, F. A., Avouac, B., Rossignol, M., Rozenberg, S., & Valat, J. P. (2005). A randomized, double-blind, placebo controlled triphosphate in study of oral adenosine subacute low back pain. *Journal of Rheumatology, 32*(6), 1114–1117.

Burnstock, G. (2007). Physiology and pathophysiology of purinergic neurotransmission. *Physiological Reviews, 87*(2), 659–797. https://doi.org/10.1152/physrev.00043.2006.

Burnstock, G., & Kennedy, C. (1985). Is there a basis for distinguishing two types of P2-purinoceptor? *General Pharmacology, 16*(5), 433–440. https://doi.org/10.1016/0306-3623(85)90001-1.

Burnstock, G., & Wood, J. N. (1996). Purinergic receptors: Their role in nociception and primary afferent neurotransmission. *Current Opinion in Neurobiology, 6*(4), 526–532. https://doi.org/10.1016/s0959-4388(96)80060-2.

Coolen, E. J., Arts, I. C., Bekers, O., Vervaet, C., Bast, A., & Dagnelie, P. C. (2011). Oral bioavailability of ATP after prolonged administration. *British Journal of Nutrition, 105*(3), 357–366. https://doi.org/10.1017/S0007114510003570.

de Freitas, M. C., Ricci-Vitor, A. L., Freire, R. V., Caperuto, E. C., Vanderlei, L. C. M., Lira, F. S., & Rossi, F. E. (2018). Oral adenosine 5'-triphosphate supplementation improved hemodynamic and autonomic parameters after exercise in hypertensive women. *Journal of Exercise Rehabilitation, 14*(4), 671–679. https://doi.org/10.12965/jer.1836256.128.

Freitas, M. C., Cholewa, J. M., Gerosa-Neto, J., Goncalves, D. C., Caperuto, E. C., Lira, F. S., & Rossi, F. E. (2019). A single dose of oral ATP supplementation improves performance and physiological response during lower body resistance exercise in recreational resistance-trained males. *The Journal of Strength & Conditioning Research, 33*(12), 3345–3352. https://doi.org/10.1519/JSC.0000000000002198.

Hayashida, M., Fukuda, K., Fukunaga, A., Meno, A., Sato, K., Tarui, K., … Hanaoka, K. (2005). Analgesic effect of intravenous ATP on postherpetic neuralgia in comparison with responses to intravenous ketamine and lidocaine. *Journal of Anesthesia, 19*(1), 31–35. https://doi.org/10.1007/s00540-004-0273-1.

Hirsch, S. P., Huber, L. G., Stein, R. A., Schmid, K., Swick, A. G., & Joyal, S. V. (2017). A randomized, double-blind, placebo-controlled study comparing the healthy levels of blood sugar and endothelial function of PEAK ATP® with GlycoCarn®, PEAK ATP® and GlycoCarn® supplementation versus placebo (Abstract). *FASEB Journal, 31*(1), 973.978.

Jäger, R., Roberts, M. D., Lowery, R. P., Joy, J. M., Cruthirds, C. L., Lockwood, C. M., … Wilson, J. M. (2014). Oral adenosine-5'-triphosphate (ATP) administration increases blood flow following exercise in animals and humans. *Journal of the International Society of Sports Nutrition, 11*, 28. https://doi.org/10.1186/1550-2783-11-28.

Jordan, A. N., Jurca, R., Abraham, E. H., Salikhova, A., Mann, J. K., Morss, G. M., … Earnest, C. P. (2004). Effects of oral ATP supplementation on anaerobic power and muscular strength. *Medicine and Science in Sports and Exercise, 36*(6), 983–990.

Ju, J., Hirose, S., Shi, X. Y., Ishii, A., Hu, L. Y., & Zou, L. P. (2016). Treatment with Oral ATP decreases alternating hemiplegia of childhood with de novo ATP1A3 Mutation. *Orphanet Journal of Rare Diseases, 11*(1), 55. https://doi.org/10.1186/s13023-016-0438-7.

Khakh, B. S., & Burnstock, G. (2009). The double life of ATP, 84–90, 92 *Scientific American, 301*(6). https://doi.org/10.1038/scientificamerican1209-84.

Kichenin, K., & Seman, M. (2000). Chronic oral administration of ATP modulates nucleoside transport and purine metabolism in rats. *Journal of Pharmacology and Experimental Therapeutics, 294*(1), 126–133.

Langen, P., & Hucho, F. (2008). Karl Lohmann and the discovery of ATP. *Angewandte Chemie (International ed. in English), 47*(10), 1824–1827. https://doi.org/10.1002/anie.200702929.

Long, G., & Zhang, G. Q. (2014). Effects of adenosine triphosphate (ATP) on early recovery after total knee arthroplasty (TKA): A randomized, double-blind, controlled study. *Journal of Arthroplasty, 29*(12), 2347–2351. https://doi.org/10.1016/j.arth.2014.03.025.

Lowery, R. P., Joy, J. M., Rathmacher, J. A., Baier, S. M., Fuller, J. C., Jr., Shelley, M. C., 2nd, … Wilson, J. M. (2016). Interaction of beta-hydroxy-beta-methylbutyrate free acid and adenosine triphosphate on muscle mass, strength, and power in resistance trained individuals. *The Journal of Strength & Conditioning Research, 30*(7), 1843–1854. https://doi.org/10.1519/JSC.0000000000000482.

Metzler, D. E. (1977). *Biochemistry: The chemical reactions of living cells*. Academic Press Inc.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Group, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Journal of Clinical Epidemiology, 62(10), 1006–1012. doi:10.1016/j.jclinepi.2009.06.005.

Moriyama, M., Kitamura, A., Ikezaki, H., Nakanishi, K., Kim, C., Sakamoto, A., & Ogawa, R. (2004). Systemic ATP infusion improves spontaneous pain and tactile allodynia, but not tactile hypesthesia, in patients with postherpetic neuralgia. *Journal of Anesthesia, 18*(3), 177–180. https://doi.org/10.1007/s00540-004-0240-x.

Phillips, S. M., Aragon, A. A., Arciero, P. J., Arent, S. M., Close, G. L., Hamilton, D. L., … Willoughby, D. S. (2017). Changes in body composition and performance with supplemental HMB-FA+ATP. *The Journal of Strength & Conditioning Research, 31*(5), e71–e72. https://doi.org/10.1519/JSC.0000000000001760.

Purpura, M., Rathmacher, J. A., Sharp, M. H., Lowery, R. P., Shields, K. A., Partl, J. M., … Jäger, R. (2017). Oral adenosine-5'-triphosphate (ATP) administration increases postexercise ATP levels, muscle excitability, and athletic performance following a repeated sprint bout. *Journal of the American College of Nutrition, 36*(3), 177–183. https://doi.org/10.1080/07315724.2016.1246989.

Rapaport, E., Salikhova, A., & Abraham, E. H. (2015). Continuous intravenous infusion of ATP in humans yields large expansions of erythrocyte ATP pools but extracellular ATP pools are elevated only at the start followed by rapid declines. *Purinergic Signal, 11*(2), 251–262. https://doi.org/10.1007/s11302-015-9450-y.

Rathmacher, J. A., Fuller, J. C., Jr., Baier, S. M., Abumrad, N. N., Angus, H. F., & Sharp, R. L. (2012). Adenosine-5'-triphosphate (ATP) supplementation improves low peak muscle torque and torque fatigue during repeated high intensity exercise sets. *Journal of the International Society of Sports Nutrition, 9*(1), 48. https://doi.org/10.1186/1550-2783-9-48.

Rossignol, M., Allaert, F. A., Rozenberg, S., Valat, J. P., Avouac, B., Peres, G., … Bannwarth, B. (2005). Measuring the contribution of pharmacological treatment to advice to stay active in patients with subacute low-back pain: A randomised controlled trial. *Pharmacoepidemiology and Drug Safety, 14*(12), 861–867. https://doi.org/10.1002/pds.1114.

Tipton, K. D., Hamilton, D. L., & Gallagher, I. J. (2018). Assessing the role of muscle protein breakdown in response to nutrition and exercise in humans. *Sports Medicine (Auckland, N. Z.), 48*(Suppl 1), 53–64. https://doi.org/10.1007/s40279-017-0845-5.

Vendelbo, M. H., & Nair, K. S. (2011). Mitochondrial longevity pathways. *Biochimica et Biophysica Acta, 1813*(4), 634–644. https://doi.org/10.1016/j.bbamcr.2011.01.029.

Wilson, J. M., Joy, J. M., Lowery, R. P., Roberts, M. D., Lockwood, C. M., Manninen, A. H., … Rathmacher, J. A. (2013). Effects of oral adenosine-5'-triphosphate supplementation on athletic performance, skeletal muscle hypertrophy and recovery in resistance-trained men. *Nutrition & Metabolism (London), 10*(1), 57. https://doi.org/10.1186/1743-7075-10-57.