Workout Extreme

Goal

To deliver an NSF Certified for Sport product with a combination of ingredients that demonstrate the ability to increase time to exhaustion or delay fatigue, especially in continuous intermittent intensity and endurance sports, while also delivering positive cognitive benefits such as improving training desire, reaction time and focus. Combining a purified caffeine (anhydrous) with glucuronolactone and clinically favorable dose of taurine may enhance the well-known performance enhancing effects of caffeine alone. Therefore, WorkoutExtreme (WE) used in individually designed doses gives the user the potential to improve training sessions and competition outcomes when compared to no supplementation or commercially available "like-products" purporting similar outcomes. While this product is designed specifically to increase time to exhaustion (prolong performance during events) for short to long event-duration endurance and intermittent athletes, WorkoutExtreme can be used by anyone not bothered by stimulants, as a pre-workout or event energy enhancement supplement.

Rationale

Exercise/activities and their respective energy systems are generalized into three categories: 1) endurance activities requiring continues submaximal muscular contractions that rely mainly on fat and glycogen stores or primarily aerobic energy; [1] 2) Strength and power activities such as weight lifting and sprinting that involve short bursts of nearly maximal muscular contractions that rely primarily on the phosphocreatine and glycolytic energy systems or anaerobic energy; [2,3] 3) high intensity interval activities common to the "intermittent athlete" (team sports that combine intermittent aerobic and anaerobic activity such as football, soccer, baseball, rugby, hockey, etc.) that require repetitive bursts of speed and power interrupted by periods of rest or low-intensity movements, thus utilizing all energy systems.[4]

The ingredients in WorkoutExtreme (WE) have been shown separately (primarily caffeine)[5] and synergistically (caffeine combined with taurine and glucuronolactone)[6] to improve performance or acute training sessions in all three categories of activities but most commonly used (clinically evaluated) in traditional endurance activities such as distant running, cycling and other medium to long continuous activity events.[5,7]

Carbohydrates (CHO) and fats are the primary substrates for energizing prolonged muscle contractions during endurance exercise with the endogenous CHO supply (glycogen stores) being a limiting factor to maximizing performance.[1] Most of the human body's glycogen resides in the liver (~100 g) and muscles (~350-750 g depending on individual physiology and diet).[8] During moderate intensity activities (30-65% of VO2 max) endogenous fat is the dominant source of energy, but as exercise intensity increases, energy contribution from carbohydrate increases and eventually becomes the most important energy source.[9] It is well established that skeletal muscle contractions are compromised during exercise leading to fatigue when glycogen stores are reduced to a certain level, although ample fuel remains from fat.[1,10] This energy phenomenon in endurance sports is commonly referred to as "hitting the wall" and therefore, the longer you can maintain glycogen stores, the longer you delay fatigue, as energy for continuous exercise cannot be produced efficiently without CHO availability.[11] Early studies demonstrated that caffeine dosing before prolonged exercise can delay fatigue and suggested its primary mechanism of action was increasing the use of fat for energy during the activity, thereby sparing glycogen.[12,13,14,15,16] Since those early studies, caffeine has been shown to improve both physical and mental performance by multiple mechanisms in a variety of activities, intensities and durations as discussed below, including shorter duration exercise (<60 minutes) when glycogen availability is not a limiting factor.[17] To be sure, substrate use during sustained high intensity exercise can be effected by caffeine,[18] but the current thinking is that caffeine's primary mechanism of action is through its ability to alter the central nervous system, including reducing ratings of perceived exertion (RPE), by blocking adenosine receptors.[19,20] Regardless of caffeine's performance enhancing mechanisms, the outcome (or the general goal) of proper supplementation is to delay fatigue in any given activity including those cognitively related.[21]

The other ingredients in WE (glucuronolactone and taurine) are contained in the product to potentially enhance caffeine's positive effects through complimentary mechanisms of actions described in their respective sections.

Caffeine

Caffeine (1,3,7- trimethylxanthine) is a methylxanthine compound formed when three methyl groups are substituted on the parent compound xanthine and is structurally related to theophylline, theobromine, and uric acid.[22] It is 100% bioavailable after oral ingestion, and is metabolized primarily in the liver producing among others, the metabolites paraxanthine, theophylline and theobromine.[23] The half-life of caffeine in healthy adults is 5-6 hours.[24] Caffeine is rapidly absorbed from the gut and transported quickly and efficiently to tissues.[25,26,27] Peak tissue concentrations of caffeine and its constituents are reached generally one hour post ingestion,[25,28] including crossing the blood brain barrier.[27,29] Based on tissue uptake and urinary clearance, tissue levels are decreased by 50-75% within 3-6 hours of ingestion.[25,30] Therefore, removal time from the bloodstream is approximately the same as caffeine's rate of absorption and metabolism.[30] Caffeine is a primary ingredient in this formula because of its positive effects on performance[30,31,32] including focus/alertness,[33,34,35] which also plays a role in training protocol motivation and success.[21,31] Caffeine anhydrous (caffeine extract without water) elicits a greater and more predictable response than caffeine delivered in caffeinated coffee, and is therefore used in this formula.[36,37]

Mechanisms of Action

Caffeine has been suggested to have multiple mechanisms of actions related to its performance and cognitive enhancing effects. Caffeine's stimulation of the central nervous system (CNS) and its ability to compete with adenosine for its receptor sites (A_1 and A_{2a}) is generally regarded as its primary ergogenic properties.[21,27,30,31,38] Because caffeine is structurally similar to adenosine, it's affinity and subsequent occupation of adenosine receptors causes a buildup of intracellular 3,5-cyclic-adenosine monophosphate (cAMP) leading to greater activity in cells.[39,40,41] Adenosine is found in every part of the body because of its role in fundamental ATP-related energy metabolism, but it has a unique brain function. Concentrations of brain adenosine are increased by various types of physical and mental metabolic stress.[23,38] Stress-related adenosine increases appear to be produced mainly by extracellular metabolism of ATP. Brain adenosine acts to protect the brain by suppressing neural activity and by increasing blood flow through A_{2A} and A_{2B} receptors located on vascular smooth muscle.[28] Caffeine elicits dis-inhibitory effects on neural activity helping to maintain or increase arousal and alertness.[25,26,27,28,38] It's conceivable that caffeine's effects are more neural than muscular since the central nervous system is a primary site of caffeine's actions.[21,41,42] The enhanced sympathetic stimulation and/or the direct adenosine antagonism by caffeine have been shown to be responsible for caffeine's glycogen sparing effects through increasing lipolysis and fat oxidation as measured by a decrease in respiratory exchanged ratio (RER) during submaximal exercise.[43,44] Cruz et al. observed these results.[45] They found, using 2.75 mg/lb of caffeine, an improvement of 22% in time to exhaustion during maximum lactate steady state (MLSS) workload, and an accompanied decrease in respiratory exchange ratio (RER), demonstrating the favorable change in energy substrate use. The lower RER observed at MLSS suggests enhanced fat oxidation and depressed carbohydrate combustion after caffeine ingestion.[45] In these and other studies, the performance improvements were based upon an increased energy reliance on fat metabolism, as shown by increased free fatty acid concentrations and lower RER.[43,44,45,46] On the other hand, Glaister et al. had participants take caffeine 1 hour before activity at 2.3mg/lb and measured its effects during submaximal exercise using multiple physiological tests including blood lactate concentrate (BLC), VO_2, RER, heart rate, ratings of perceived exertion (RPE) and minute ventilation.[20] The main finding, using a sophisticated testing protocol, was that caffeine compared to placebo *stimulated glycolysis* as shown by increases in BLC independent of exercise intensity but must have still been due to an increase in lactate efflux from the working muscles, therefore, supporting recent theories that caffeine's primary mechanisms are most likely related to its complex central and peripheral effects associated predominantly with the antagonism of the various adenosine receptors subtypes and leading to a corresponding increase in intracellular cyclic adenosine monophosphate.[7,17,18,19,20,30,31] In this case, a direct effect on skeletal muscle through the antagonism of A_1 adenosine

receptors. Additionally, in this Glaister et al. study, they showed that the caffeine group suppressed RPE as in previous reports[47]. These main outcomes (glycogen stimulating/BLC and suppressed RPE) combined with significant multiple respiratory effects, give credence to caffeine's multifactorial whole body effects that primarily appear driven by changes in the central and peripheral nervous systems, especially when you consider it's positive ergogenic effects across many ranges of intensities during both long and short-term activities, including when the compartmentalization of energy use appears unchanged compared to placebo during successful trials .[18,20,31,48,49]
The metabolites of caffeine mentioned above also contribute to caffeine's effects. Paraxanthine is responsible for an increase in the lipolysis process, releasing glycerol and fatty acids into the blood to be used as fuel by the muscles, thus potentially sparing glycogen.[27,50] Theobromine is a vasodilator that increases the amount of oxygen and nutrient flow to the brain and muscles.[41] Theophylline acts as a smooth muscle relaxant that chiefly affects bronchioles and acts as a chronotrope and inotrope that increases heart rate and efficiency.[51,52]
And finally, Cappelletti et al. makes a case that caffeine's effects on physical performance may also be related to the release of calcium from the sarcoplasmic reticulum and inhibition of its reuptake, reactions that would lead to increases nitric oxide through the activation of endothelial nitric oxide synthase (NOS).[53] The authors surmise that these actions may be associated with changes in neuromuscular function and increased contractile force in skeletal muscles[53,54]

Caffeine Mechanism and Dosing Summary

Summarizing caffeine's proposed performance enhancing mechanisms of action, studies have reported caffeine ingestion increases mobilization of free fatty acids (FFA),[12,13,14,15,18,43,44,45,46] spare glycogen,[12,13,14,15,43,44,45,46,50,51] stimulate the release of epinephrine and β-endorphins[50] (may decrease pain perception[55,56]), block the effects of adenosine,[20,21,31,56,57] alter the calcium level in muscle,[53,54] possibly increase blood pressure in non-habitual users[58] and stimulate the central nervous system.[21,49,59,60,61,62,63] All of these physiological effects may also explain caffeine's ability to reduce fatigue[20,47] improve concentration,[21,64,65] and enhance mental alertness.[21,58,66,67,68,69,70,71,72]
The bottom line is caffeine can stimulate physical and mental activities while delaying fatigue or feelings of exertion. Whether caffeine accomplishes this outcome through alterations in energy compartment use or "overriding" normal fatiguing factors through its adenosine receptor agonist actions on the central and peripheral nervous systems (e.g. directly and indirectly promoting the release of various neurotransmitters), may not be important to the many users since caffeine is considered safe and may yield health benefits (at least through coffee/tea delivery). However, actual mechanisms matched to specific outcomes may be of great interest to the scientist and future applications.

Dosing (also see below for caffeine dosing in sports and testing): Using 1.4-3 mg/lb of caffeine in an anhydrous state (delivered by coffee ~1.36-3.68 mg/lb[7]) 30-60 minutes before activity, there is universal agreement that caffeine supplementation can enhance different modes of exercise performance[20,21,45,31,47,73,74] including endurance,[7,31,36,37,45,75,76,77,78,79] high intensity team sport activity of long duration, (e.g. rugby, soccer, hockey etc.)[31,49,58,80,81,82,83,84] strength, muscle power and muscle endurance (primarily anaerobic).[57,58,74,85,86,87,88,89] In the latter group, Chen et al. found no gender differences in the ergogenic effect of caffeine[88] and Trexler et al. found coffee delivery of caffeine to be as effective as caffeine anhydrous.[89] In a lower dose application used among golfers, approximately 1mg/lb caffeine improved measures of performance and reduced fatigue in skilled golfers.[90]

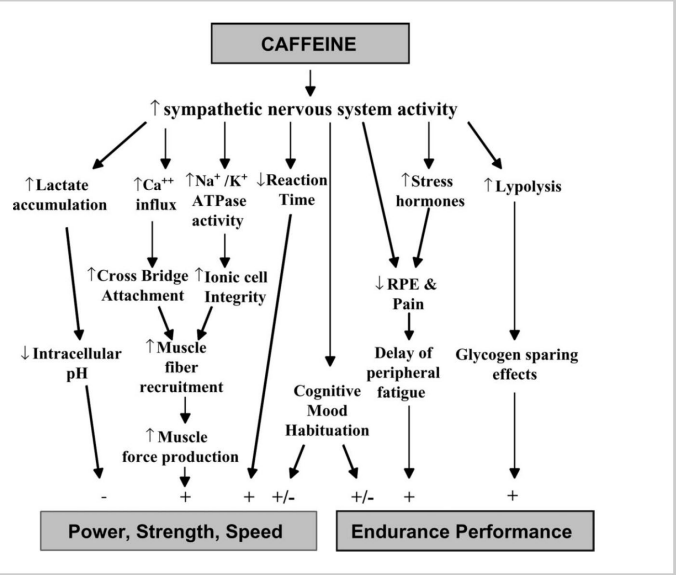
Responders and Non-responders

Like with all studies using supplements (or prescription drugs) there are caffeine investigations that showed little to no improvement in different performance measures in individuals and overall.[31] These results are generally attributed to dosing formulations (anhydrous or not), true non/less-responders (genetics [e.g. slow caffeine metabolism], lifestyle and habitual use[91]), type of activity, or study end-point measured. Some reports have discovered up to 30% of caffeine study participants derived little to no ergogenic benefits.[92,93] In fact, Womack et al. may have identified a genetic polymorphism as a primary reason for some people not deriving an ergogenic effect from caffeine supplementation.[94]

Using 2.75 mg/lb in a 40-kilometer time trial, performance in cyclists homozygous for the A variant (of the cytochrome P450 gene –faster caffeine metabolism) had a greater performance increase than those who possess the C variant (slower caffeine metabolism). Caffeine decreased 40-km time by an average of 3.8 minutes in the AA homozygotes as compared to 1.3 minutes in the C allele carriers highlighting a specific polymorphism as a potential cause of variations in the performance effect of caffeine supplementation.[94] Polymorphisms of the ADORA2A gene (codes for A_2 receptors) may also influence individual responses to caffeine's stimulating effects.[95,96]

Caffeine Supplementation Effects on Physical Performance

Clearly caffeine supplementation can improve performance across multiple activities, sports and protocols with caveats listed above. Despite early reports of caffeine's performance enhancing mechanisms being attributed to its stimulatory effects on free fatty acid release and sparing glycogen, thus considered predominately an endurance exercise ergogenic aid, the primary mechanism is currently considered to be its ability to activate the CNS via its role in blocking adenosine receptors (e.g. A_1 and A_2) as described above.[21,31] Therefore, caffeine's effects on physical performance are now discovered in: 1) muscle strength and power, 2) prolonged endurance activities, 3) high intensity exercise and intermittent sports; 4) perceived exertion and pain related to delaying fatigue (see Figure 1 from Sokmen et al.[97] with permission).



Potential mechanisms of caffeine in endurance and power events.

Figure 1
Caffeine's potential mechanisms of action through its stimulation of the CNS (adenosine receptor blockage) as depicted by Sokmen et al. with permission.

Muscle Strength, Endurance and Power, and Team Sports

This category would include anaerobic activities (muscle strength and endurance) and high intensity interval activities common to the "intermittent athlete" (team sports that combine intermittent aerobic and anaerobic activity such as football, soccer, baseball, rugby, hockey, etc.) that require repetitive bursts of speed and power interrupted by periods of rest or low-intensity movements, thus utilizing all energy systems.

In the category of anaerobic activities, McLellan et al. reported that two-thirds of the 33 trials related to muscle strength and endurance, found an ergogenic effect of caffeine.[21] Caffeine's potential to increase anaerobic outcomes is often associated with its purported ability, at high doses, to enhance intracellular Ca^{2+} release leading to increased contractility and force generation.[53,54,98,99] But at some level, it also appears caffeine's other direct CNS effects contribute to the improvements seen in muscle strength and endurance.[48,100,101]

When caffeine ingestion improves intermittent high intensity activities including team sports, almost with certainty multiple mechanisms of actions described above are at play, including alterations in energy compartment pathways.[21,45,47,102]

Related Studies

- Ajmol et al., using 2.75 mg/lb of caffeine anhydrous, examined the supplement's effects versus placebo on knee flexor and knee extensor strength before, during, and after intermittent running exercise in female team-sport players. The caffeine group, compared to placebo, significantly enhanced eccentric muscle strength and power during and following intermittent running exercise. Additionally, eccentric knee flexor power and strength remained significantly elevated the following morning. The authors concluded: "caffeine supplementation increased eccentric strength and power in female team-sport players both during an intermittent running protocol and the following morning."[49]
- Turkish coffee (TC) generally has more caffeine than equal amounts of typical western world coffees because the TC preparation method (no drip) leaves a greater amount of biologically active components, including caffeine.[103] Church et al.[104] investigated a low dose (1.4 g/lb) of Turkish coffee versus decaffeinated coffee (DC) on the reaction time and time trial performance of 20 male and female subjects. The results showed that plasma caffeine concentrations were significantly elevated within 30 minutes post TC ingestion. Subjects consuming TC had significantly greater reaction performance and subjective feelings of energy. Although no significant differences were found in time trial performance, 60% of participants (12/20) ran faster during the 5-km time trial using TC compared to DC. When comparisons between TC and DC were performed in the responders only, the time differentials between trials were significantly different. This percentage of responders (habitual coffee drinkers possessing a gene associated with enhanced cytochrome P450 1A2 and faster caffeine metabolism[105,106]) is consistent with other studies as described above.
- Talanian et al. tested in a bout of 120 minutes of cycling, a low (100 mg) and moderate (200 mg) dose caffeine and carbohydrate (CHO) solution ingested late in exercise (after 80 minutes of cycling at 60% peak oxygen interspersed with 40 second and 120 second intervals at ~80%). Following the 120-minute cycling challenge, cyclists completed a 0.7 calorie/lb body mass (-1) time trial. The moderate caffeine time trials were completed faster (26:36) than the low, (27:36) and both caffeine time trials finished faster than placebo (28:41). Authors concluded, both doses of caffeine delivered late in exercise improved time trial performance over the placebo trial and the moderate dose improved performance to the greatest extent.[107]
- Boyett et al. assessed caffeine supplementation benefits on cycling performance based on time of day (morning and evening) and training status (trained and untrained subjects) using 2.75 mg/lb in time trials. The study demonstrated both time of day and training status effected outcomes. Caffeine enhanced the 3-km time trial performance to a larger degree in the morning than evening for all subjects, but the greater improvement was found in the untrained participants at both times. Little benefit was found in trained subjects during evening testing. The authors concluded with, "observations indicate that trained athletes are more likely to derive ergogenic effects from caffeine in the morning than the evening. Untrained individuals appear to receive larger gains from caffeine in the evening than their trained counterparts." Furthermore, by measuring peak strength changes between placebo and caffeine treatment, they also noted that the improvement from caffeine supplementation in time trial performance was not mediated by improvements in strength.[108]
- Higgins MF et al. evaluated the effects of consuming sodium bicarbonate (NaHCO3) or caffeine individually or in combination on high-intensity cycling capacity. 60 minutes prior to exercise, test subjects either consumed 1) 0.14 g/lb of body mass sodium bicarbonate (BIC); 2) 2.3 mg/lb of body mass of caffeine plus 0.045 gm/lb sodium chloride (CAF); 3) .67 gm/lb sodium bicarbonate plus 2.3 mg/lb caffeine (BIC-CAF); or 4) 0.45 gm/lb sodium chloride (placebo). Time of cycling to volitional exhaustion at 100% Wpeak, was significantly greater for CAF and BIC-CAF compared to BIC but not compared to placebo. There were no differences in placebo and BIC or between CAF and BIC-CAF. The authors found a large inter-and intra-individual variation when comparing treatments suggesting what appears obvious, that caffeine supplementation requires an individual approach in delivering benefits.[109,110]

- Diaz-Lara et al. studied the effectiveness of a moderate dose (1.4 mg/lb) of caffeine or placebo, to enhance overall performance during a simulated Brazilian jiu-jitsu (BJJ) competition. Specific strength and power tests were performed before the first combat session and immediately after the first and second combats along with measures of blood lactate. In all cases, after caffeine ingestion, subjects spent more time in offensive actions in both combats and had higher blood lactate values, suggesting a higher lactate threshold. Performance in all physical tests before the first combat were enhanced with caffeine, with improvements continuing after the first combat, such as maximal static-lift test and bench press. After the second combat, the physical tests were similar between caffeine and placebo. The authors concluded caffeine may be effective for improving intensity during successive combat bouts.[111]
- Further extending the study of the BJJ competitors consuming the 1.4 mg/lb of caffeine versus placebo, Diaz-Lara et al. found that the caffeine users increased dynamic and isometric muscular force, power, and endurance strength.[112]
- More related to body composition, in a double-blind, randomized placebo-controlled trial performed to detect the potential thermogenic effect of a caffeine polyphenolic supplement (CP), Jo E et al. tested (a) metabolic rate and fat oxidation at rest and after a 30min bout of sprint interval exercise (SIE), and (b) SIE performance. The CP treatment resulted in significantly greater energy expenditure (+7.99% rest; +10.16% post-SIE), VO_2 (+9.64% rest; +12.10% post-SIE), and fat oxidation rate (+10.60% rest; +9.76% post-SIE) vs. placebo at rest and post-SIE. No significant differences were found for peak and average power at all sprint intervals between treatments. Post-SIE heart rate was significantly greater with CP vs. placebo (90.8 ± 3.5 vs. 85.1 ± 3.6b·min) with no significant between-treatment differences for blood pressure. The authors concluded that "the observed thermogenic response after SIE was directly attributable to the CP as opposed to an indirect manifestation of enhanced performance and work output." The results appear to support the use of caffeine and polyphenols in efforts to reduce body fat and improve body composition when combined with exercise.[113]
- Highton J et al. examined the effects of carbohydrate (CHO) and caffeine on performance versus CHO alone among rugby players. Using 40 g of CHO with 1.4 g/lb of caffeine (C-CHO), 8 rugby players completed two trials of a rugby simulation protocol seven days apart measuring movement characteristics, heart rate, ratings of perceived exertion (RPE), and countermovement jump height (CMJ). The (C-CHO) tests were significantly better that CHO alone:
    - Higher mean running speeds: effect size (ES) 0.43 to 0.75; distance in high intensity running ES 0.41 to 0.64; and mean sprint speeds ES 0.39 to 1.04
    - Higher heart rate: ES 0.32 to 0.74
    - Lower RPE: ES -0.53 to 0.86
    - Tendency towards higher CMJ: ES 0.07 to 0.25

  Authors conclusion: "The co-ingestion of carbohydrate with caffeine has an ergogenic effect to reduce the sense of effort and increase high intensity running capability that might be employed to enhance interchange running performance in elite rugby league players.[114]
- Wellington et al. also found performance improvements (repeat high intensity effort) in rugby players using 300 mg of caffeine pre-exercise.[84]
- In another caffeine combination, double blind placebo controlled study, this time with essential amino acids (EAA), Eaton et al. examined the ability of EEA (2x7 g) and caffeine (1.4 g/lb) to attenuate central nervous system fatigue during a simulated team sport-specific running protocol in a hot, hypoxic environment on four separate tests. The subjects consumed 1 of 4 supplements: a placebo, caffeine + placebo, EAA + placebo, or caffeine + EAA before each exercise session using a randomized, double blind crossover design. The EAA + caffeine trials tested superior in all tests including higher mean sprint work. The decline in electromyography (EMG) activity was less as was the central activation ratio and cerebral oxygenation. The conclusion: co-ingestion of caffeine and EAA appears to

maintain muscle activation and central drive, with a small improvement in running performance when compared to placebo, caffeine or EAA alone in a hot hypoxic environment.[115]

- Portillo et al. tested caffeine (1.4 mg/lb), but this time in an energy drink versus the same drink without caffeine, on skills and technical performance during a match in female elite rugby sevens players. The authors found the ingestion of the caffeine energy drink increased the number of body impacts, suggesting higher player engagement during competition but noticed no effect in the quality of the technical actions performed. A common theme from the use of caffeine appears throughout team sports is that competitive desire or motivation may be increased with relatively low doses.[116]
- Albeit a small study, Ribeiro et al. had six male handball athletes consume 2.7 mg/lb of caffeine (CAF) or placebo (PLA) on two different occasions. 60 minutes following intake, all participants performed a protocol of vertical jumps (VJs) consisting of four sets of 30 seconds of continuous VJs with 60 seconds of recovery between sets. Blood lactate (BL) and creatine kinase (CK) levels were measured before and after the protocol. CAF resulted in a 5.23% improvement in the leg power compared with PLA, along with higher BL (6.26 vs. 4.39 mmol/L respectively) after VJ protocols whereas no difference in CK was observed between trials - suggesting no extra muscle damage although greater work was performed during the CAF test. This led the authors to conclude: "nutritional interventions with caffeine could help athletes withstand a greater physiological overload during high-intensity training sessions and may be applicable to sports and activities that require repetitive leg power."[117]
- Lara et al. used a caffeinated energy drink (CED) containing a relatively low dose of caffeine (1.4 mg/lb) to test its effects on performance in sprint swimmers in a randomized counterbalance order. Compared to the placebo drink (P), the CED increased the height in the countermovement jump (49.4 vs. 50.9 cm, respectively) and maximal force during the handgrip test. Additionally, CED reduced the time needed to complete the 50-meter simulated swimming competition (27.8 vs. 27.5 sec) and resulted in increased peak power (273 vs. 303W) and blood lactate concentration during the ergometer test. The study revealed the CED increased aspects of swimming performance with virtually no side effects at this dose.[118]
- Bloms et al. found 2.2 mg/lb of caffeine versus placebo (P) increased squat jump height (32.8 ± 6.2 vs. 34.5 ± 6.7 cm), counter movement jump (CMJ) height (36.4 ± 6.9 vs. 37.9 ± 7.4 cm), peak force, and average rate of force development. It appeared that caffeine affected both height and execution of jumping. Therefore, the authors concluded: "The physical mechanism of jump enhancement suggests that the ergogenic effects of caffeine may transfer to other ballistic tasks involving the lower-body musculature in collegiate athletes."[74]
- Chen et al. found supplementing 2.75 mg/lb of caffeine compared to placebo, significantly increased maximal voluntary isometric contractions (MVIC) and submaximal voluntary isometric contractions, and concluded that these ergogenic effects of caffeine (muscle power and endurance) had no gender bias.[88]

Endurance Performance

Caffeine supplementation has been shown to enhance endurance performance. Mclellan et al. captured 59 caffeine and endurance activity studies and showed that in 46 of these, caffeine significantly improves exercise performance.[21] As mentioned above, contrary to early reports that caffeine's effect on endurance was primarily related to alterations in substrate utilization (increase fatty acid usage versus glycogen, thus sparing glycogen), the more highly regarded mechanism of action is now considered caffeine's activation of the CNS from adenosine receptor (A_1 and A_{2a}) blockage.[21,27,30,31,38,119] Caffeine and adenosine are received the same into the A2a receptors and therefore caffeine can occupy the space, thus blocking adenosine (which would otherwise curb activity between nerves cells)[28] from reaching the same destination subsequently promoting an excitatory potentiation of D2 receptors and increasing psychomotor activity.[21,120]

Optimal doses for endurance performance results appear to be between 1.4-3.2 mg/lb taken 60 minutes before activity.[21] Time to peak caffeine circulating concentrations can vary drastically (0.5-3 hours) between individuals,[121,122] but caffeine's ergogenic effects can persist for several hours throughout the plasma concentration range[78,121] with circulating concentrations of ~15-20 µM.[5,21]

Perceived Exertion and Muscle Pain

Reduced ratings of perceived exertion (RPE)[78,79,37] and/or sensations of muscle pain[21,123,124] during or following performance exercise trials using caffeine supplementation (CA) are often associated with the trials enhanced performance outcome.[20,21,31,47] These additional effects of caffeine supplementation can contribute to its ability to increase exercise intensity and total work, as well as increase time to exhaustion, and are probably tied to the CA adenosine blockade function. [21,27,30,31,38] Clearly adenosine levels increase during strenuous muscle activities[125] and when adenosine binds to the A_1 receptor site pain is induced.[126] Therefore, a significant portion of caffeine's ergogenic effects may be from its ability to mitigate the body's normal signals to slow down including CA antinociception properties (inhibition of A_1-, A_{2A}-and A_3Rs – i.e. receptor blockade leading to reduced pain[127]). In a meta-analysis by Doherty et al. it was surmised that caffeine's ability to reduce RPE might accomplish up to 30% of the measured improvement during constant load exercise trials.[47] Duncan et al pointed out that along with reduced RPE, caffeine raised arousal and affective states, which may also contribute to its ergogenic effects.[123]

Related Studies

- Caldwell et al. had participants use 1.4 mg/lb of caffeine (CA) versus placebo (P) and investigated ratings of perceived muscle soreness (RPMS) and perceived lower extremity functionality (LEF) following the completion of a 164-km endurance cycling event. CA and P were ingested immediately after the ride and for the next four mornings (~800 hours) and three afternoons (~1200 hours). Prior to each ingestion, RPMS and LEF were assessed. Results were that afternoon ratings of LEF were greater with CA but only the first day post ride. Further, the CA subjects tended to have lower overall RPMS in the afternoon. The authors concluded: "ingesting caffeine improved RPMS for the legs, but not LEF in the days following an endurance cycling event. Athletes may benefit from ingesting caffeine in the days following an arduous exercise bout to relieve feelings of soreness and reduced functionality."[128]
- Suvi et al. used 2.75 mg/lb of caffeine (CA) versus placebo to compare the physical performance and psychological effects of CA in men and women exercising in the heat. They concluded CA ingestion increased heart rate and blood lactate levels during exercise in the heat, but it had no impact on thermoregulation or endurance capacity in either sex. Under exercise-heat stress, caffeine reduces ratings of perceived exertion and fatigue in males but not in females.[129]
- Cheng et al. used 2.75 mg/lb of caffeine (CA) compared to placebo (P) to test basketball players on a 3-minute all-out test (3MT) on performance and their plasma electrolytes. 60 minutes after ingestion, the subjects performed the 3MT to estimate the end-test power (EP) and work done above EP (WEP). Compared to P, the CA condition produced significantly higher power outputs (60-150 seconds), a lower fatigue rate during the 3MT (CA .024 vs. .029 seconds), significantly higher lactate concentration after the 3MT, significantly lower potassium (K(+)) concentrations at one hour after CA, and no significant interaction effects for pH and sodium (Na(+)) concentrations. Conclusion: "caffeine ingestion did not change EP, but improved work done above end test power (WEP) and the rate of decline in power output during short-term, severe exercise."[130]
- Green et al. found, compared to placebo, 2.75 mg/lb of caffeine to improve cycling cadence (4 revs/min faster) at a lower rate of perceived exertion (RPE 4 vs. RPE 7).[131] The small study and mild effects may have to do with responders versus non-responders. Green et al. found using the same RPE and dosage protocol that subjects improved treadmill velocity performance at both RPE 4 and 7 (~5 m/min faster).[132]
- Gonglach et al. found similar results as Green et al. in that CA compared to P increases work performed during exercise eliciting a moderate amount of pain, but found that a threshold level of pain may exist where the CA adenosine receptor blockade induced pain reduction may be ineffective at increasing work.[56]
- Stadheim et al. tested placebo (P) versus 2.05 g/lb of caffeine (CA) on double poling (DP) performance during acute hypoxia. During submaximal exercise, CA participants reported lower pain in arms and lower rate of perceived exertion (RPE). The study showed that CA improves DP time to task failure but not consistently time trial

performance during acute exposure to altitude. Improvement mechanisms appeared to be related to decreases in RPE and increased heart rate during the 8-km cross country DP time trial.[133]

- Smirmaul et al. examined the effects of 1.9 mg/lb of caffeine (CA) or placebo (P) on performance, neuromuscular fatigue and perception of effort on seven cyclists during high-intensity cycling exercise in moderate hypoxia. They found CA delivered a 12% improved time to exhaustion, a significant decrease in subjective fatigue, a lower perception of effort and higher heart rate compared to P. Concluding: "the caffeine-induced improvement in time to exhaustion during high-intensity cycling in moderate hypoxia appears to be mediated by a reduction in perception of effort, which occurs despite no reduction in neuromuscular fatigue.[134]
- Graham-Paulson et al. studied the effects of 1.9 mg/lb of caffeine (CA) on cycling and hand-cycling (lower and upper body activities) on 10-km time trial (TT) performance in regular caffeine users. Compared to P, CA significantly improved cycling (16:35 vs. 16:56 min) but not hand-cycling TT performance. The CA vs. P improvement during lower body activity (cycling) was attributed to increased power output during the first and last two kilometers and was accompanied with higher blood lactate concentration. CA also produced lower overall ratings of perceived exertion (RPE) during the preload but not post-TT. The CA test also showed lower peripheral RPE in both cycling and during hand-cycling. While CA improved cycling TT performance, it did not significantly improve hand-cycling, leading the authors to surmise that CA many not affect smaller muscles such as arms the same as larger lower body muscles.[135] This may relate to the fact that arms have a greater proportion of type II fibers than legs,[136] and type II fibers are shown to be less sensitive to caffeine ergogenic effects.[137]

Caffeine in Life Including Health, Cognitive Performance

It is beyond the scope of this article to discuss details on how caffeine is used and effects different aspects of life including occupational and basic cognitive performance. The reader is referred to the McLellan et al. review article: *A review of caffeine's effects on cognitive, physical and occupational performance,* for a comprehensive look at caffeine's effects in these areas.[21]

Caffeine is one of the world's most commonly consumed drug, food and supplement.[138] Approximately 85% of U.S. adults regularly ingest caffeine with the majority being consumed as coffee.[139] There is universal agreement that caffeine consumption of up to 400 mg day (or ~2.5 mg/lb) in healthy adults is not only classified as "considered safe," but also associated with health benefits including enhanced fat metabolism,[140] and reduced risk of disease, at least when delivered by coffee or tea.[141,142] However, like many other universally ingested substances, caffeine is not for everyone based primarily on its stimulatory effects that can cause acute adverse reactions in susceptible sub-populations[143,144] (see Adverse Event section below).

Caffeine's general effects on an individual's "state of being" including cognitive performance are well established at standard doses ranging from 50-400 mg:

- Positive influence on mood[143,145]
- Improved reaction times and alertness[66,69,70,71,145]
- Euphoric sensations[146]
- Maintenance of cognitive and physical performance (dosing at approximately 200 mg every two hours) during drastic sleep deprivation [71,147]
- Following exhaustive activities, CA increases cognitive task performance including Stroop and Rapid Visual Information Processing Tasks[75] and has been shown to prevent central fatigue related decrements in oculomotor control (eye movement muscles)[148]
- Positive effects on age-related cognitive impairments through CA antagonistic effect on A_{2A} Receptors and subsequent modulation of glucocorticoid receptors[149]
- Enhance memory consolidation in humans[150,151] and improve memory performance in young adults[64]

Caffeine Myths, Diuretics, Abstaining, Fluid Balance, etc.

Misconceptions abound regarding ingested substances that can induce significant changes in human health and performance, including caffeine.

Diuresis, Hydration, Fluid and Electrolyte Balance

Caffeine's (CA) most misunderstood characteristic is likely its impact in body fluid balance. Unfortunately, people often confuse caffeine the supplement, with caffeine as the constituent of a fluid delivery system such as coffee, tea, energy drinks, sodas, etc., which all contain primarily water. Therefore, between the normal effect of any fluid intake on diuresis and an individual's hydration status before ingestion, hydration would be minimally affected by the caffeine content in the fluid – i.e. more fluid intake leads to more urine output; the less hydrated at the onset of coffee/tea etc. intake, the less urinary output.

To highlight this, Maughan et al. using 72 subjects, investigated the effects of 13 commonly ingested drinks on urine output and fluid balance when consumed in a euhydrated state, to establish a beverage hydration index (BHI), i.e., the volume of urine produced after drinking expressed relative to a standard treatment (still water) for each beverage.[152] Cumulative urine output at four hours after ingestion of cola, diet cola, hot tea, iced tea, coffee, lager, orange juice, sparkling water, and a sports drink were not different from the response to water ingestion, indicating caffeine content had no effect on hydration outside the delivery system. The CA in the caffeine containing drinks ranged from 96-212 mg/L.[152] However, caffeine is known to inhibit the release of arginine vasopressin,[153] which could increase urinary output but that might normally happen at regular doses > 300 mg and only *at rest*.[154] None of the latter applies to caffeine and exercise, but the facts pointing to normal caffeine intake not affecting hydration in either direction as shown here by Maughan et al., mirrors the same result found with CA use during exercise, i.e., there is no significant effect on hydration, fluid balance or electrolytes and therefore no contraindication related to hydration and exercise.[31] Along these lines, Wemple et al. used a total dose of 4 mg/lb of CA and found an increase in urine volume at rest but no difference in fluid balance with CA during exercise.[155]

Falk et al. found no differences in total water loss or sweat rate following consumption of a 3.4 mg/lb dose of caffeine and treadmill walking with a 48 lb backpack at an intensity of approximately 70-75% VO_2 max.[156]

Other researchers have established the same outcomes[157,158] including during heated conditions.[159,160] Roti et al. found that chronic supplementation of 1.4-2.75 mg/lb of CA did not negatively affect sweat rates, fluid-electrolyte balance, thermoregulation or performance.[159] Millard-Stafford et al. also found CA did not affect hydration in heated conditions but improved long duration performance in highly trained endurance athletes.[160]

A review by Armstrong et al. on this subject stated: "caffeine consumption does not result in the following: (a) water-electrolyte imbalances or hyperthermia and (b) reduced exercise-heat tolerance."[161]

A meta-analysis by Zhang et al. (median dosage was 300 mg) on CA and diuresis concluded: "caffeine exerted a minor diuretic effect which was negated by exercise. Concerns regarding unwanted fluid loss associated with caffeine consumption are unwarranted particularly when ingestion precedes exercise."[162]

Habitual Use – Abstaining

The evidence relating to an abstention period before administering CA to improve performance is not equivocal but does favor the side of being unnecessary.[21,17,31] Clearly, daily consumers of caffeinated drinks experience similar individually specific daily CA ingestion outcomes or feelings such as changes in alertness, mood, wakefulness, potential tremors, reaction times, etc.[71,143,145,147,150,151] Therefore, the drug's related mechanisms of action must be at play regardless of consumption regularity.[21,163,164] Whether the CA exercise performance enhancing effects are greater from a period of abstaining or not may also be individually specific, although Irwin et al. found that regular users of CA (light to heavy daily consumption) had similar ergogenic effects regardless of days of abstinence.[163,164] On the other hand, Beaumont et al. investigated 4 weeks of 1.4 mg/lb of CA supplementation on endurance performance in 18 low-habitual caffeine consumers (<75 mg/day). All subjects performed more work compared to placebo, but the performance benefit was no longer apparent after four weeks of CA supplementation while the placebo group

retained benefits. The authors concluded: "chronic ingestion of a low dose of caffeine develops tolerance in low-caffeine consumers," suggesting individuals with low-habitual intakes refrain from chronic CA supplementation to maximize acute CA ingestion performance benefits.[165]

While Bell et al. found CA to enhance performance in both regular (≥300 mg/d) and non-users of caffeine (≤50 mg/d), the non-users' CA performance enhancement lasted approximately three hours longer.[78] Other researchers found no performance enhancement differences between daily CA users and non-users, but non-users show other biomarker changes such as heart rate, tremors, plasma epinephrine levels, etc.[166,167,168]

Considering all the data, it seems prudent for individual experimentation with CA supplementation. Therefore, an athlete using CA as an ergogenic aid should test its overall performance effect under both conditions: 1) ingest the designated dose on the event day (60 minutes before exercise) following 3-5 days of abstaining; 2) maintain normal daily CA intake and use the same performance dosing protocol on event day. Measuring overall effects on pre-event state of being (e.g. readiness, energy levels, etc.), work production and quantitative event outcome under both conditions should determine the athletes preferred protocol.

Caffeine and Regulations in Sports

Caffeine supplementation (CA) at 1-4 mg/lb of body weight taken 30-60 minutes before exercise is an effective performance enhancing aid for many athletes and their respective activities as discussed throughout this article. While most users have no reason to be concerned about how much caffeine they ingest within recommended safety limits, the acceptable caffeine limit for NCAA athletes is 15 micrograms per milliliter (15 µg/ml) urine.[169] The NCAA doesn't actually test for CA at this time, as they concede caffeine to be too common a part of everyday life, although caffeine remains a listed monitored ingredient.[170] The International Olympic Committee (IOC) allows up to 12 µg/ml in urine before the substance is considered illegal.[171] According to The American College of Sports Medicine (ACSM), a person weighing 154 pounds consuming 5 to 6 regular size cups of coffee (each 8-12 oz), approximately one hour before a workout, would have a urinary caffeine level approaching the IOC limit.[171] In terms of milligrams (mg), it would require approximately 600-900 mg of caffeine (depending on individual metabolism and size) to be consumed within two hours of urine testing to potentially reach the IOC deemed illegal urine level. Therefore, a 175-pound athlete (with normal caffeine metabolism) using a higher end recommendation of CA (3 mg/lb or ~525 mg) of caffeine one hour before competition should have a urine concentration <12 µg/ml. However, as a disclaimer, everyone metabolizes caffeine differently, meaning IOC drug tested athletes should experiment with doses and testing if they choose to use CA beyond 2 or 3 cups (8 oz each) of regularly brewed coffee.[78,94,95,96]

For readers interested in caffeine content in popular drinks, we refer you to The Caffeine Chart webpage from The Center for science in The Public Interest[172] CSPI.

Data Summary

Caffeine exerts its effects by occupying adenosine receptors throughout the CNS and other body tissues leading to a cascade of events that collectively work to enhance cognitive and physical performance under both normal or energy/sleep deprived conditions. CA supplementation is dose dependent with significant variation in individual responses (e.g. responders, non-responders, fast and slow metabolizers). The ergogenic effects of caffeine have been demonstrated across a wide variety of exercise activities including high intensity and anaerobic tests of power, agility, speed and muscular endurance that may transfer to related team sports; delay fatigue in endurance sports; and improvement in time trials. Caffeine does not upset fluid balance or induce diuresis during exercise.

Dosing

- *Caffeine's effects on cognitive performance (alertness, vigilance, memory, etc.) are generally experienced at relatively lower doses such as .25-2 mg/lb of body weight.*
- *Dosages that induce improvements in exercise performance range from 1.4-3 mg/lb of body weight (not to exceed 600 mg) and taken approximately one-hour pre-activity.*

- *Except under unique circumstances, doses greater than 4.1 gm/lb of body weight deliver no further benefit*
- *For exercise performance, caffeine in the anhydrous form is preferred based on the ability to accurately assess and control the dosing*
- *CA supplementation within recommended doses is considered safe for healthy individuals*
- *Competitors should experiment with dosing described here during practice sessions to personalize their most effective protocol including testing abstention for two to four days*

Glucuronolactone, Caffeine and Taurine

This combination of ingredients is common in energy drinks.[6,118,173] The reason they are included in this product with caffeine is for their potential additive effects to focus and performance/recovery. Based on solid evidence, it is easy to argue caffeine is the only ingredient of these three that delivers the desired effects described in the caffeine section above –i.e. mental/cognitive and/or physical performance improvements. However, studies using this combination have demonstrated similar success with a lower caffeine content, suggesting a possible additive (especially taurine) or at least a synergistic effect allowing lower caffeine doses, which may be important to certain caffeine sensitive individuals. Additionally, there appears to be little to no safety concerns with this combination.[6,118,173]

Taurine

Taurine (2-aminoethanesulfonic acid) is a semi-essential amino acid found in mammalian tissues that is not involved in protein synthesis.[174] The function of taurine is not completely understood but it is known that taurine modulates intracellular Ca^{2+} levels.[175] In skeletal muscle, its main roles are to facilitate Ca^{2+} dependent excitation contraction processes, contribute to the regulation of cellular volume, and aid in antioxidant defense from stress responses.[176,177,178] Its potent antioxidant role may contribute to its potential benefits in patients with heart failure.[179] Taurine also is involved in retinal photoreceptor activity, bile acid conjugation, white blood cell antioxidant activity, central nervous system neuromodulation, platelet aggregation, cardiac contractility, sperm motility, growth, insulin activity,[180] and osmoregulation.[181]

Related Mechanism of Action

Dutka et al. studied taurine's (T) effects on sarcoplasmic reticulum Ca^2 (SR Ca^2) accumulation and contractility in human type I and II fibers in skeletal muscle, which is thought to be taurine's primary potential performance enhancing mechanism of action.[182] The study demonstrated that prolonged myoplasmic exposure to taurine (>10 minutes) significantly increases the rate of SR Ca^2 accumulation in both type I (which contains ~ 2 to 3 times more taurine than type II[183]) and II muscle fibers probably through taurine's actions in the sarcoplasmic reticulum lumen – i.e. most likely the result of taurine modifying sarcoplasmic reticulum $Ca2^+$-ATPase (SERCA) function from enhancing its maximum pumping rate and/or increasing its affinity for Ca^{2+} (See Figure 2) Therefore, it is believed that taurine supplementation can enhance performance due to a greater ability to generate power through enhanced calcium regulation[184,185] by helping maintain maximum levels that would improve muscle contractile properties when taurine is otherwise at low physiological levels.[6,182] Finally, there have been reports that taurine interacts with certain neurotransmitter receptors in the CNS.[186,187]

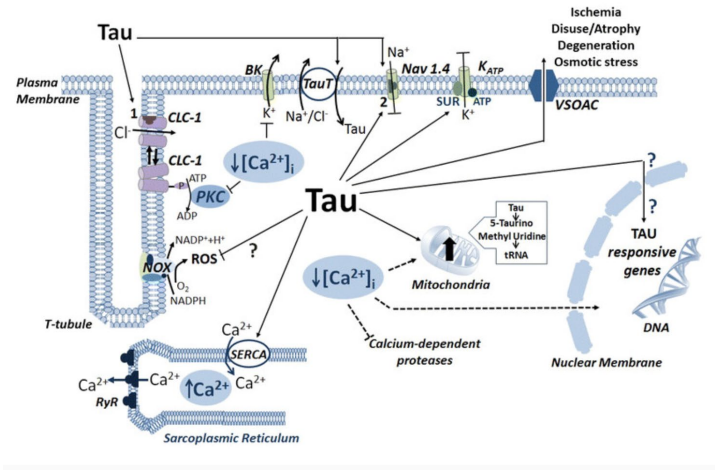


Figure 2 – Depiction of taurine's effects on modifying sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) function leading to enhanced calcium regulation, which under certain conditions, supplementation may lead to improved performance.[184] Image adapted from De Luca et al. and used per open access. [184]

Generally, in purported energy products, taurine is used in combination with other ingredients such as caffeine, glucuronolactone, and carbohydrates. Studies are equivocal on the independent effect of taurine supplementation (TS) on muscle performance, but supplementation studies using one to six grams of taurine have yielded positive results related to muscle function, recovery[188,189] and endurance performance.[190,191]
Rutherford et al. found using 1.6 grams of taurine one hour before exercise did not increase time trial performance in well trained cyclists, but significantly increased fat oxidation (16% over 90 minutes).[192] Da Silva et al. showed taurine supplementation increased strength and decreased muscle soreness, lactate dehydrogenase levels, creatine kinase activity, and oxidative damage, but did not decrease the eccentric exercise inflammatory response following the activity.[193] The Song-Gyu Ra et al. study suggested using a combination of 3.2 g of branched chain amino acids (BCAA) and 2.0 g taurine, three times a day, for two weeks prior to and three days after exercise, to be useful for attenuating exercise-induced delayed onset muscle soreness (DOMS) and muscle damage.[194]
Milioni et al. found an acute dose of 6 g of TS before exercise did not substantially improve high-intensity running performance and showed an unclear effect on alternative maximal accumulated oxygen deficit (MAODALT).[195]
Ward et al. found that a pre-exercise dose of 1,000 mg of taurine delivered no performance advantage during 4 km cycling time trials (TT) nor did it alter the blood buffering responses in trained cyclists.[196] Contrary to Ward, Balshaw et al. found a 1.3 % improvement in 3 km TT running performance in well trained middle-distance athletes using an acute ingestion of 1,000 mg of taurine.[184]

In summary, TS in isolation has produced inconsistent performance enhancing effects at all ranges of doses but probably gives rise to its inclusion in many energy drink (ED) formulas. To this point, Souza et al. in a systematic review and meta-analysis (34 studies) on the effects of ED on physical performance found that the degree of improvement was associated with the taurine dosage. The author's conclusion: "The review and meta-analysis showed that ED intake improved performance in several physical and sport situations that included muscle strength protocols, jumping, endurance exercise tests and sport-specific action, and taurine dosage influenced the outcome."[6] The caffeine dosages ranged from 40 to 325 mg and taurine ranged from 71 to 3,105 mg. Compared to caffeine and taurine doses used in isolation for enhancing performance, the facts from this study appear to support a synergistic relationship between the two compounds in that the dosages found in these EDs were each generally lower but yielded similar benefits.[6,173]
And lastly, related to taurine in combination with caffeine, Warncok et al. studied caffeine (C), taurine (T), caffeine and taurine co-ingestion (C+T) or placebo (P) on repeated Wingate cycling performance and associated physiological responses.[197] Using C at 2.3 mg/lb of body weight, T at 22.25 mg/lb of body weight, C+T at 2.3 mg and 22.75 mg, P at 22.25 mg/lb of body weight, all supplements increased mean peak power (MPP), peak power (PP) and mean power

(MP) compared to P, with greater MPP, PP and MP in T compared to C. Additionally C and C+T increased heart rate (HR), mean arterial pressure (MAP) and rate pressure product (RPP) compared to P and T at baseline but only remained higher in C compared to all conditions in the final sprint. Conclusion: "Taurine elicited greater improvements in performance compared to P, C or C+T, while reducing the typical chronotropic and pressor effects of caffeine (C)." While this latter study may not support an increase in performance through the synergy of caffeine and taurine compared to either in isolation, it does suggest that taurine at 3-4 grams one hour prior to exercise may be an effective performance dose and that the non-result from the addition of caffeine could be that dosage performance thresholds of each in the C+T trial were achieved and no further benefit attainable by combining the two. To this point, the difference between taurine and caffeine plus taurine was small to possible but certainly makes a case for taurine.[197]

Glucuronolactone

Glucuronolactone is a naturally occurring chemical that is an important structural component of nearly all connective tissues and found in many plant gums.[198] In the body, glucuronolactone is metabolized to glucaric acid, xylitol, and L-xylulose, and humans may also be able to use glucuronolactone as a precursor for ascorbic acid synthesis.[199] According to *The Merck Index*, it is also used as a detoxicant. The liver uses glucose to create glucuronolactone, which causes blood-glucuronide levels to rise. Glucuronides combine with toxic substances, by converting them to water-soluble conjugates, which are excreted in the urine.[200] Hypothetically, higher blood-glucuronides should help remove toxins from the body, leading to the claim that energy drinks are detoxifying. We make no such claims. Its presence in this product (WorkoutExtreme), as mentioned above, is for any potential synergistic effect based on empirical data.[173] On this note, Miles-Chan et al. tested the non-caffeine bioactive ingredients in sugar free Red Bull (SFRB) against water and caffeine (WC). Their results were: SFRB and WC both increased REE to the same degree (+4%). But only SFRB briefly increased respiratory quotient (RQ) suggesting a temporary increase in carbohydrate oxidation that may have been due to the non-caffeine ingredient synergies (e.g. 240 mg/glucuronolactone and 800 mg/taurine).[201]
Although levels of glucuronolactone in energy drinks generally far exceed those found in standard diets, the European Food Safety Authority (EFSA) concluded that exposure to glucuronolactone from regular consumption of energy drinks is not a safety concern. The no-observed-adverse-effect level of glucuronolactone is 1,000 mg/kg/day.[202]

Energy Drinks Including Caffeine, Taurine and/or Glucuronolactone in Combination

All though these three ingredients are common in popular energy drinks (ED), relatively few studies have investigated formulas with caffeine, taurine and glucuronolactone in combination.[173] There are no studies that we know of that has firmly established an additive cognitive or physical performance contribution of taurine or glucuronolactone beyond caffeine's benefits notwithstanding Warnok et al.[197] As mentioned, studies using this combination with caffeine have documented safety and efficacy but performance enhancements may have been likely due to the caffeine content[173] and possibly taurine.[6] Noting that studies supporting ED performance benefits (increased mental focus/cognitive performance,[6,203] reaction time and physical endurance) generally used formulas that contained lower caffeine levels (between ~0.5 to 1.5 mg/lb) than positive studies using caffeine alone (1.4-2.75 mg/lb), tends to lend credence to the claim of a potential synergistic effect from glucuronolactone and taurine.[6,204,205,206,207]
Positive studies using lower levels of caffeine content in ED, found increases in training/lifting volume but not necessarily absolute power.[205,208,209] To this point, Del Coso et al. had 12 male and female non-resistance trained subjects use a commercially available ED with either .45 mg or 1.4 mg/lb caffeine or a placebo one hour before the test.[210] Each participant completed 10-to-100% 1 repetition max (1-RM) power-load tests for the bench press and half-squat. The .45 mg/lb of caffeine was not enough to raise the power output. However, the group using the ED with 1.4 mg/lb of caffeine increased maximal power output by 7% in the half-squat and bench-press compared to placebo.[210] Gonzalez et al. found that an ED containing caffeine, taurine and glucuronolactone ingested 10 minutes before a workout resulted in an 11.9% improvement in number of repetitions during four sets of the squat or bench press using 80% of the participants 1-RM.[211] Additionally, the average power output for the workout was significantly higher for

subjects consuming the ED compared to placebo users.[211] Alford et al. found aerobic performance was 8-14% longer compared to carbonated water following the ingestion of a popular ED.[204] Ivy et al. using an ED containing ~1 g/lb of caffeine found that the ED group finished the time trial ~4.7% faster than the placebo subjects.[212] Walsh et al., using an energy mix (2.05 g of caffeine, taurine, glucuronolactone), amino acids (7.9 g of L-leucine, L-isoleucine, L-valine, L-arginine and L-glutamine), di-creatine citrate (5 g), and β-alanine (2.5 g) 10 minutes before activity, investigated the effects on aerobic performance and subjective measures of focus, energy, and fatigue in active male and females. Participants consuming the ED increased time to exhaustion while running at 70% of VO_2 max by 12.5%, reported greater focus, energy, and less fatigue before exercise. Their ratings of focus and energy were also greater 10 minutes into exercise.[213]

Prins et al. evaluated exercise performance time and related physiological responses of recreational endurance runners using Red Bull (ED) containing caffeine, glucose, and taurine. Performance improved with ED compared with placebo (ED: 1,413.2 vs. PLA: 1,443.6 seconds), but no differences in ratings of perceived exertion (RPE), or the distance covered at 5-minute splits between the two 5 km time trials.[214]

The bottom line is that caffeine dosing is effective for improving cognitive and physical performance and glucuronolactone and taurine do not appear to depress caffeine's well known effects and may produce a synergistic effect that would allow a lower dose of caffeine to produce higher dose effects.[6,173] Additionally, as Souza et al. found in the meta-analysis described above, taurine appears to be the primary ingredient, and possibly in a dose-dependent manner, that enhances the outcomes of energy drinks with formulas similar to WorkoutExtreme when compared to placebo.[6]

Summary

At the very minimum, NSF Certified for Sport WorkoutExtreme contains the clinically proven performance enhancing dose (including dosing instructions) and form of caffeine shown to improve training and competition results in a wide variety of anaerobic, aerobic/endurance activities and team sports (intermittent athletes) compared to a non-supplemented state. The addition of taurine in clinically favorable doses (3,000 mg) along glucuronolactone may enhance caffeine's well-known ergogenic benefits, ratings of perceived exertion, delaying fatigue effects and cognitive benefits, and possibly allow greater results at lower dosages.

Typical Use

- Adults exercisers/athletes not bothered by stimulants seeking to delay fatigue, prolong and improve performance during events:
    - Short to long event-duration/endurance activities (running, cycling, etc.)
        - Five (5) capsules 40-60 minutes before activity (totaling 350 mg caffeine) unless caffeine sensitive, in which case start with two (2) capsules and adjust as necessary or;
        - Use 1.4 to 3 mg/lb of body weight (not to exceed 600 mg) take 40-60 minutes before activity
        - If competing, experiment to achieve proper dose and abstain from all caffeine including WorkoutExtreme two to four days before competition
    - Intermittent athletes, such as football, baseball, soccer, hockey, rugby, swimming, etc.
        - Five (5) capsules 40-60 minutes before activity (totaling 350 mg caffeine) unless caffeine sensitive, in which case start with two (2) capsules and adjust as necessary
- Any adult not bothered by stimulants, as a pre-workout or event energy enhancement supplement or as a daily pick-me-up. Take as directed.
- If using regularly, it is recommended to cycle use three weeks on and at least one week off or use only as needed before activities.
- Should not be taken within four (4) hours of other products containing stimulants (especially caffeine) such as coffee, energy drinks, etc. or mixed with other stimulants.

Precautions

WorkoutExtreme™ contains central nervous system (CNS) stimulants and should be avoided by those sensitive to caffeine or who are contraindicated for caffeine-containing supplements or adverse to any other ingredient in WorkoutExtreme. Do not mix with other stimulants, especially bitter orange[215] or ephedra.[216] As noted, caffeine has no significant effect on hydration, fluid balance or electrolytes and therefore no contraindication related to hydration and exercise.[31,154,155,156]

Contraindications

WorkoutExtreme™ supplementation is contraindicated in pregnancy and lactation because of caffeine content at higher dosage[217] and because studies are not performed using this population with other ingredients. Taurine and caffeine can interfere with some medications such as lithium[218] and MAO inhibitors.[219] While caffeine consumption does not increase the risk of developing hypertension,[220] caffeine is contraindicated in hypertension, anxiety and thyroid disease.[38] Caffeine is also contraindicated in those with cardiac arrhythmias, other forms of heart disease and peptic ulcers. [221] Caffeine should not be mixed with beta-agonists since theoretically, concomitant use of large amounts of caffeine might increase cardiac inotropic effects of beta-agonists.[222] Do not mix with diuretic drugs. Theoretically, excessive amounts of caffeine in combination with diuretics may increase the risk of hypokalemia.[223] Although evidence that caffeine ingestion causes cardiac arrhythmias is inconclusive, individuals should consult with their physician first before using WorkoutExtreme.[224]

Adverse Reactions

Caffeine: use may result in slight diuresis (increased water loss, usually in non-regular users) and insomnia when taken late in the day. Numerous studies on the safety of caffeine exist.[31, 225] Caffeine abuse can cause tension, anxiety, excitability and restlessness at doses over 400 mg at one time.[225] Doses over 1,000 mg at one time can elicit toxicity symptoms.[224,226] WorkoutExtreme has only 350 mg but adverse effects may occur in sensitive individuals. Taking WorkoutExtreme with other stimulants is not advised unless separated by at least four (4) hours. Adverse effects due to high amounts of caffeine are not likely to occur at the recommended dose of WorkoutExtreme.[31,225] Individuals sensitive to caffeine may wish to start with a low dose and work up to the recommended dose.

Taurine: Taurine is an amino acid naturally present in many foods, especially meats and fish. It has been combined with caffeine in several beverage studies with no adverse events reported except in one study where a mild increase in mean arterial blood pressure (2.8 mm Hg average) and an eight-beat-per minute reduction in heart rate were shown.[203,227,228] Taurine is used for congestive heart failure at higher doses from two to six grams daily to help increase stroke volume with few side effects such as mild diarrhea.[229] It is also used for other disease states such as hepatitis and cardiac arrhythmias where doses from 12 to 20 grams daily were used.[229] Mild diarrhea was reported in a few subjects in the heart failure studies. People enrolled in research studies have not reported any significant side effects connected with the use of taurine.[6,172,179,189,230]

Glucuronolactone: Glucuronolactone is a substance found in many caffeine and taurine containing energy drinks at doses of 500 mg or more per drink. It is considered safe and well-tolerated in these beverages.[204,231] The European Food Safety Authority (EFSA) concluded that exposure to glucuronolactone from regular consumption of energy drinks is not a safety concern. The no-observed-adverse-effect level of glucuronolactone is 1,000 mg/kg/day.[202]

Upper Limit/Toxicity

Caffeine: should not exceed 1,000 mg/day, [224,226] leaving the dose in WorkoutExtreme at a safe level.[31,225]

Taurine: Taurine has an LD50 in rats of greater than 64g/kg and therefore practically unattainable.

Glucuronolactone: the no-observed-adverse-effect level of glucuronolactone is 1,000 mg/kg/day.[202]

Summary

Purpose

- Deliver an NSF Certified for Sport product with a combination of ingredients that demonstrate the ability to increase time to exhaustion or delay fatigue and reduce perceived exertion, especially in continuous intermittent intensity exercise (team sports such as football, basketball, soccer, rugby, etc.) and endurance sports (running, cycling, etc.).
    - Recommended dosing gives the user the potential to improve training sessions and competition outcomes when compared to no supplementation.
- Deliver positive cognitive benefits such as improving training desire, reaction time and focus
- For any adult not bothered by stimulants, as a pre-workout or event energy enhancement supplement
- Should not be mixed with other stimulants or used within five hours before sleep, or by people adverse to any stimulants.

Unique Features

- A rare combination of clinically effective doses of both caffeine anhydrous and taurine where taurine may significantly amplify caffeine's well-known performance enhancement effects
- Uses a rapid release capsule delivery system to maximize the formula's potential and provide a timely impact on training intensity
- Ideal dosing instructions for any activity
- NSF Certified for Sport (NSFCS), an independent third-party test which provides an additional product guarantee to ensure purity and potency for drug tested athletes. Click here for the dotFIT NSFCS section.
- Manufactured in a regularly inspected NSF certified facility, in compliance with Good Manufacturing Practices (GMPs) exclusively for dotFIT, LLC

Supplement Facts Panel

Supplement Facts

Serving Size: 2 Capsules — Servings per Container: 75

	Amount Per Serving	% DV
Taurine	1200 mg	*
Glucuronolactone	240 mg	*
Caffeine Anhydrous	140 mg	*

* % Daily Value not established.

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