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Functional Dose-Response Effects of Adrenaline on Skeletal Muscle Performance (PHASE II)

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ABSTRACT

Background: Adrenaline enhances skeletal muscle performance during stress and exercise, but the dose-response relationship and underlying mechanisms remain incompletely characterized.

Objective: To investigate the dose-response effects of adrenaline on skeletal muscle fatigue resistance and identify the optimal functional dose.

Methods: Frog gastrocnemius-sciatic nerve preparations were treated with saline (Control) or adrenaline at 0.01, 0.1, 0.5, or 1.0 mg/kg. Contractile function (n=40) and biochemical parameters including energy metabolites, glycogenolytic enzymes, signaling molecules, and ionic regulators (n=30) were measured. Integrated analyses including correlation, multiple regression, and path analysis were performed.

Results: Adrenaline produced significant dose-dependent improvements in force generation (+26%), fatigue resistance (T50 +49%), and recovery capacity (+32%), with maximal effects at 0.5 mg/kg. Biochemical analyses revealed increased phosphorylase activity (+20.3%), cAMP elevation (+41.2%), decreased PCr/Pi ratio (-15.5%), and enhanced Na^+/K^+-ATPase activity (+5.9%). The 1.0 mg/kg dose showed diminished effects across 78% of parameters, confirming a biphasic inverted-U relationship. Multiple regression identified plasma adrenaline and PCr/Pi ratio as the strongest predictors of fatigue resistance (R^2=0.87). Path analysis confirmed a hierarchical mechanism: Adrenaline → β_2-receptor → cAMP → Phosphorylase → PCr/Pi → Functional improvement.

Conclusion: Adrenaline enhances skeletal muscle fatigue resistance through integrated β_2-adrenergic signaling, metabolic activation, and ionic regulation. The optimal dose (0.5 mg/kg) produces maximal functional benefits, while supra-maximal doses reduce efficacy through receptor desensitization and metabolic overload. These findings provide a mechanistic framework for understanding catecholamine modulation of muscle function.

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Introduction

Adrenaline is a critical catecholamine hormone that orchestrates the "fight-or-flight" response, preparing the body for increased physical demands. During intense exercise or stress, circulating adrenaline levels rise substantially, triggering a cascade of physiological adaptations including increased heart rate, enhanced cardiac output, bronchodilation, and mobilization of energy substrates [1,2].

In skeletal muscle, adrenaline exerts its effects primarily through β_2-adrenergic receptors, activating the cAMP-PKA signaling pathway. This leads to enhanced glycogenolysis, increased calcium release from the sarcoplasmic reticulum, and improved force production [3,4]. However, the dose-response relationship between adrenaline and muscle function has not been systematically characterized, particularly regarding fatigue resistance and recovery capacity. Understanding this relationship is clinically relevant for conditions characterized by muscle fatigue, including chronic fatigue syndrome, heart failure, and neuromuscular disorders.

Moreover, the potential therapeutic application of adrenergic agonists requires precise knowledge of the optimal dose window to maximize benefits while minimizing adverse effects. The frog gastrocnemius-sciatic nerve preparation has been a classical model for studying muscle physiology since the work of Galvani and later Sherrington. Its advantages include well-characterized contractile properties, ease of experimental manipulation, and the ability to maintain stable preparations for extended periods [5,6].

Adrenaline also modulates muscle metabolism in ways that influence fatigue resistance. It stimulates glycogenolysis, enhances glucose uptake, and increases lactate output from contracting muscle (Stainsby et al., 1987). In the dog gastrocnemius-plantaris muscle, epinephrine infusion has been shown to stop the decline of oxygen consumption (VO_2) during repetitive contractions, indicating a protective effect against the metabolic deterioration associated with fatigue (Stainsby et al., 1987). Furthermore, studies using adrenergic receptor antagonists have demonstrated that α- and β-receptors interact in a complex manner to modulate fatigue, with β-receptors increasing lactate output while α-receptors exert an inhibitory effect (Stainsby et al., 1987). Despite this substantial

body of evidence establishing adrenaline as a modulator of skeletal muscle contractile function and metabolism, a critical gap remains in the literature: the dose-response relationship between adrenaline concentration and its effects on muscle fatigue resistance has not been systematically characterized. While some studies have employed single doses or narrow concentration ranges, and others have investigated dose-dependent metabolic effects such as energy expenditure (Stainsby et al., 1987), no comprehensive dose-response analysis has been performed specifically examining adrenaline's impact on the fatigue resistance of the gastrocnemius muscle across a physiologically relevant concentration spectrum. Understanding this relationship is essential, as adrenaline's effects on the cardiovascular system are known to be strongly dose-dependent low doses produce β_2-mediated vasodilation, whereas higher doses elicit α_1-mediated vasoconstriction and similar biphasic or threshold effects may exist for skeletal muscle fatigue modulation. Therefore, the present study aims to systematically investigate the dose-response relationship of adrenaline on the fatigue resistance of the gastrocnemius muscle. By exposing isolated or in situ gastrocnemius preparations to graded concentrations of adrenaline and assessing contractile function during fatiguing stimulation protocols, this research will elucidate the concentration-dependent effects of this critical stress hormone on muscle endurance. Such findings have important implications for understanding the physiological regulation of muscle performance during exercise and stress, as well as for optimizing therapeutic strategies that target adrenergic pathways in conditions characterized by muscle weakness or fatigue.

Dose-Response Considerations

Despite the well-documented effects of adrenaline on muscle function, the dose-response relationship remains incompletely characterized. Available evidence suggests that adrenaline's effects are concentration-dependent, but the shape of the dose-response curve including the threshold for detectable effects, the concentration eliciting maximal response, and the potential for biphasic or inhibitory effects at supraphysiological doses has not been systematically established for muscle fatigue resistance. Some studies have provided partial insights regarding dose-dependent effects. For instance, metabolic effects such as oxygen uptake and lactate production have been shown to vary with adrenergic stimulation (Stainsby et al., 1987). However, these findings primarily reflect systemic effects and do not directly address the dose-response relationship at the level of the muscle itself. Furthermore, the concentrations of adrenaline used in in vitro experiments have varied considerably, ranging from 10^{-7} mM to higher in vivo doses, making direct comparisons challenging.

Research Objectives

To investigate the physiological mechanisms through which adrenaline modulates skeletal muscle performance" To identify the optimal functional dose of adrenaline that enhances skeletal muscle performance.

Research Questions

Which physiological mechanisms through which adrenaline modulates skeletal muscle performance What are the optimal functional dose of adrenaline that enhances skeletal muscle performance.

Adrenaline as a Physiological Modulator of Muscle Function

Adrenaline is a catecholamine hormone synthesized in the adrenal medulla and released into the systemic circulation in response to sympathetic nervous system activation. Alongside noradrenaline, it constitutes the primary humoral effector of the classic "fight-or-flight" response, orchestrating a coordinated suite of physiological adaptations—increased cardiac output, bronchodilation, redistribution of blood flow, and mobilization of metabolic substrates that prepare the organism for acute stress or vigorous physical exertion . During exercise, circulating adrenaline levels rise in proportion to exercise intensity, with significant elevations observed above approximately 50–70% of maximal oxygen consumption [1]. The actions of adrenaline on skeletal muscle are mediated through two principal classes of adrenergic receptors: β-adrenergic receptors (predominantly the β_2 subtype) and α-adrenergic receptors. β_2-receptor stimulation activates the adenylyl cyclase–cyclic adenosine monophosphate (cAMP)–protein kinase A (PKA) signaling cascade, which phosphorylates key regulatory proteins involved in calcium handling, metabolism, and contractile function [7]. This pathway is responsible for the well-documented potentiating effects of β-adrenoceptor agonists on peak twitch and tetanic tension, as well as their defatiguing effects on skeletal muscles [4].

The Frog Gastrocnemius as an Experimental Model

The gastrocnemius muscle of the frog has been extensively utilized as a model for studying skeletal muscle physiology, pharmacology, and fatigue mechanisms [8]. As a mixed-fiber-type muscle containing both fast-twitch glycolytic (type II) and slow-twitch oxidative (type I) fibers, it provides a representative platform that mirrors the heterogeneous fiber composition of many human skeletal muscles. The muscle is readily accessible for in situ experimentation, its well-defined anatomy permits precise measurement of contractile parameters during controlled stimulation protocols, and its blood supply can be manipulated to investigate the relationship between perfusion and metabolism. Previous investigations have characterized the β-adrenergic signal transduction system in the rat gastrocnemius and demonstrated its responsiveness to endurance training. Moreover, the gastrocnemius has been employed in studies examining the glycogenolytic effects of adrenaline in different muscle fiber types, the role of epinephrine in exercise-induced metabolic responses, and the impact of adrenergic agonists on muscle fatigue characteristics. These foundational studies establish the frog gastrocnemius as an appropriate and well-validated model for investigating the dose-response relationship of adrenaline on muscle fatigue resistance.

Metabolic Effects of Adrenaline in Skeletal Muscle

Adrenaline exerts profound effects on skeletal muscle metabolism, particularly on carbohydrate metabolism. It stimulates glycogenolysis through activation of phosphorylase, the rate-limiting enzyme in glycogen breakdown. Injection of epinephrine in rats causes a marked rise in the phosphorylase a content of muscle. Furthermore, epinephrine prevents the complete disappearance of phosphorylase a in fatigued muscle and accelerates the resynthesis of phosphorylase a during recovery from fatigue.

The glycogenolytic effect of adrenaline in skeletal muscle depends on the type of muscle fiber. Górski found that in resting rats, adrenaline exerts the least glycogenolytic effect in white (fast-twitch glycolytic) muscle and the greatest effect in intermediate (fast-twitch oxidative-glycolytic) muscle. A dose of 0.1 mg/kg adrenaline produced a cumulative effect with exercise on glycogen levels in white muscle, whereas in red and intermediate muscles, exercise-induced glycogen depletion was so rapid that no additional effect of adrenaline was observed. A higher dose of 0.5 mg/kg adrenaline prevented glycogen repletion in both red and intermediate muscles during recovery.

The role of epinephrine in glycogenolysis during exercise has been investigated using adrenodemedullated (ADM) rat models. Winder et al. demonstrated that ADM rats show a marked reduction in endurance run times compared with sham-operated controls. Glycogenolysis was impaired in ADM rats in the fast-twitch white region of the quadriceps, lateral gastrocnemius, and soleus muscles. Infusion of epinephrine into ADM rats during exercise corrected hypoglycemia, restored lactate to normal, and stimulated glycogenolysis in soleus, white quadriceps, and lateral gastrocnemius muscles. This epinephrine-dependent glycogenolysis in contracting type I and noncontracting type II muscle fibers provides essential quantities of lactate for hepatic gluconeogenesis in fasted exercising rats.

However, the relationship between epinephrine and glycogenolysis during intense contraction is not straightforward. Some studies have concluded that high physiological concentrations of epinephrine are not important for enhancing glycogenolysis in rat muscles composed predominantly of fast-twitch fibers during intense short-term tetanic stimulation [9]. This suggests that the metabolic effects of adrenaline are context-dependent, varying with contraction intensity, muscle fiber type, and the metabolic state of the muscle (McConell et al., 2005). Adrenaline also modulates oxygen consumption and lactate metabolism in contracting muscle. Stainsby et al. (1987) investigated adrenergic receptor-mediated responses in the dog gastrocnemius-plantaris muscle during repetitive, isotonic, tetanic contractions. In control experiments, contractions increased oxygen consumption (VO_2) to approximately 50 times rest by 2 minutes, after which shortening, work, and VO_2 declined together by 17% at 30 minutes, indicating muscle fatigue. Epinephrine infusion stopped the decline of VO_2 during contractions, an effect not observed with other agonists. Propranolol (a β-blocker) decreased VO_2 compared with controls, while phenoxybenzamine (an α-blocker) also decreased VO_2. Both epinephrine and isoproterenol increased lactate output compared with controls; this epinephrine response was antagonized by propranolol but enhanced by phenoxybenzamine. These findings demonstrate that β-receptor activation increases lactate production, whereas α-receptor activation inhibits it (Stainsby et al., 1987).

Dose-Response Considerations

Despite the substantial body of evidence establishing adrenaline as a modulator of skeletal muscle contractile function and metabolism, the specific dose-response relationship for its effects on muscle fatigue resistance remains incompletely characterized. Available evidence suggests that adrenaline's effects are concentration-dependent, but systematic dose-response analyses are lacking. Some studies have provided partial insights. Górski demonstrated that a dose of 0.1 mg/kg adrenaline had a cumulative effect with exercise on glycogen depletion in white muscle, whereas a dose of 0.5 mg/kg prevented glycogen repletion in both red and intermediate muscles. These findings indicate dose-dependent metabolic effects, with higher doses exerting more pronounced and longer-lasting effects on glycogen metabolism. In the context of endurance performance, studies using capsaicin-induced adrenal catecholamine secretion in mice have demonstrated dose-dependent improvements in swimming endurance. The maximal effect was observed at a dose of 10 mg/kg, while more than 15 mg/kg had no additional effect. This observation suggests the existence of an optimal dose beyond which further increases in adrenaline concentration do not confer additional benefit—a pattern consistent with a saturable or biphasic dose-response relationship.

The dose-response relationship is further complicated by the opposing actions of adrenaline mediated through different receptor subtypes. Low concentrations may preferentially activate high-affinity β_2-receptors, producing vasodilation and metabolic stimulation. At low infusion rates, epinephrine predominantly activates β_2-adrenergic receptors in peripheral vasculature, particularly in skeletal muscle and skin [10]. Higher concentrations engage α-receptors, which can cause vasoconstriction and potentially limit oxygen and substrate delivery. We hypothesized that adrenaline would produce a biphasic (inverted-U) dose-response relationship in skeletal muscle, with moderate doses enhancing contractile performance and fatigue resistance, while supra-maximal doses would produce diminished benefits due to excessive metabolic demands and receptor desensitization.

Materials and Methods

Ethical Approval

All experimental procedures were approved by the Institutional Animal Care and Use Committee and complied with the guidelines for the care and use of laboratory animals.

Animals

Forty adult frogs (Rana temporaria) weighing between 100-120 g were obtained from a commercial supplier. Animals were housed in controlled environmental conditions (22-24°C, 12:12 light-dark cycle) with access to water ad libitum. Food was withheld for 24 hours prior to experiments to standardize metabolic conditions.

Experimental Design

Frogs were randomly assigned to five treatment groups (n=8 each):

- Control: 0.9% saline (vehicle)
- Low: 0.01 mg/kg adrenaline
- Moderate: 0.1 mg/kg adrenaline
- High: 0.5 mg/kg adrenaline
- Supra: 1.0 mg/kg adrenaline

Adrenaline (Sigma-Aldrich, St. Louis, MO) was prepared fresh daily in 0.9% saline and administered via the dorsal lymph sac in a volume of 0.1 mL/100g body weight. Control animals received an equivalent volume of saline.

Surgical Preparation

Frogs were anesthetized by immersion in 0.1% tricaine Methanesulfonate (MS-222) solution buffered to pH 7.0 with sodium bicarbonate. Anesthesia was confirmed by loss of withdrawal reflex and corneal reflex. The right gastrocnemius muscle with attached sciatic nerve was dissected free of surrounding tissues while maintaining vascular supply. The distal tendon was attached to a force transducer (FT-03, Grass Instruments, Quincy, MA) with a silk suture. The sciatic nerve was placed on a bipolar stimulating electrode (Model S48, Grass Instruments). Core body temperature was monitored with a rectal thermistor and maintained at 22-24°C using a heated water bath.

Stimulation Protocol

Muscles were stimulated supramaximally (1.5× threshold, 0.2 ms pulse duration) using the following protocol:

- **Baseline twitch:** Single pulses at 1-minute intervals for 10 minutes
- **Tetanic stimulation:** Trains of 500 ms duration at 100 Hz
- **Fatigue protocol:** 0.5 Hz stimulation for 300 seconds or until force declined to 50% of baseline

Recovery assessment: Post-fatigue twitch measurements at 1, 2, 3, 4, 5, 10, 15, 20, 25, and 30 minutes

Data Acquisition

Force signals were amplified, digitized at 1 kHz, and recorded using LabChart Pro software (ADInstruments, Colorado Springs, CO). The following parameters were calculated:

Primary Outcomes

- Peak twitch tension (g)
- Peak tetanic tension (g)
- T50: Time to reach 50% of initial peak tetanic force (s)
- Force decline: Rate of force decrease during fatigue protocol (%/min)
- Recovery force: Force at 30 minutes post-fatigue (g)
- Recovery ratio: Recovery force / Pre-fatigue twitch force
- Rate of contraction: Maximum rate of force development (g/s)
- Rate of relaxation: Maximum rate of force decline (g/s)
- Ergographic effect: Area under the fatigue curve

Secondary Outcomes

- Heart rate: Measured via electrocardiogram (bpm)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Core temperature (°C)

Statistical Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp, Armonk, NY). Normality was assessed using Shapiro-Wilk test. Homogeneity of variances was confirmed with Levene's test. One-way ANOVA was performed followed by Tukey's HSD post-hoc test for multiple comparisons. Linear and quadratic regression analyses were conducted to characterize dose-response relationships. Effect sizes were calculated using eta-squared (η^2). Pearson correlation coefficients were computed between parameters. Statistical significance was set at $p<0.05$. Data are presented as mean ± SD unless otherwise specified.

Results

Animal Characteristics

No significant differences were observed among groups for body weight ($F=0.21$, $p=0.931$) or core temperature ($F=1.43$, $p=0.244$) (Table 1). Baseline physiological parameters were consistent across groups, confirming successful randomization.

Table 1: Showing Baseline Physiological Parameters

Parameter	Control (n=8)	Low (n=8)	Moderate (n=8)	High (n=8)	Supra (n=8)	F	p
Weight (g)	111.5 ± 6.2	112.6 ± 6.4	110.8 ± 5.7	110.6 ± 6.3	110.1 ± 7.4	0.21	0.931
Temperature (°C)	23.6 ± 0.9	22.8 ± 0.8	23.7 ± 0.8	23.2 ± 1.1	23.1 ± 0.6	1.43	0.244

Data presented as mean ± SD

Peak Twitch Tension

Adrenaline produced a significant dose-dependent increase in peak twitch tension ($F=108.4$, $p<0.001$, $\eta^2=0.92$) (Table 2, Figure 1A). Post-hoc analysis revealed that the Low dose did not significantly differ from Control ($p=0.067$), whereas Moderate, High, and Supra doses all produced significant increases ($p<0.001$). The High dose (0.5 mg/kg) produced maximal effect (+26.9%), while the Supra dose showed a 9.6g reduction compared to High ($p=0.002$).

Table 2: Peak Tetanic Tension

Group	Peak Twitch (g)	% Change	95% CI
Control	100.6 ± 3.0	-	98.0-103.2
Low	105.7 ± 4.2	+5.1	102.7-108.7
Moderate	115.0 ± 2.8	+14.3	112.6-117.4
High	127.7 ± 1.5	+26.9	125.2-130.2
Supra	118.1 ± 2.0	+17.4	116.2-120.0

The quadratic regression model ($R^2=0.84$, $p<0.001$) provided a significantly better fit than the linear model ($R^2=0.71$, $p<0.001$), confirming the inverted-U shape (Figure 2A).

Peak Tetanic Tension

Similar to twitch responses, peak tetanic tension showed a significant dose-dependent increase ($F=153.2$, $p<0.001$, $\eta^2=0.94$) (Table 3, Figure 1B). The High dose produced maximal enhancement (+26.0%), significantly greater than all other groups ($p<0.001$). The Supra dose showed a 25.0g reduction compared to High ($p<0.001$), confirming the biphasic pattern.

Group	Peak Tetanic (g)	% Change	95% CI
Control	300.7 ± 7.5	-	296.7-304.7
Low	313.4 ± 6.1	+4.2	308.9-317.9
Moderate	347.0 ± 9.9	+15.4	339.5-354.5
High	378.9 ± 5.6	+26.0	373.6-384.2
Supra	353.9 ± 7.6	+17.7	349.0-358.8

Quadratic regression significantly improved model fit ($R^2=0.88$ vs linear $R^2=0.74$, $p<0.001$) (Figure 2B).

Time to Fatigue (T50)

Adrenaline produced a robust, dose-dependent prolongation of T50 ($F=139.7$, $p<0.001$, $\eta^2=0.93$) (Table 4, Figure 1C). All doses significantly increased T50 compared to Control, with the High dose (+49.3%) producing maximal effect. The Supra dose showed a 16.4s reduction compared to High ($p<0.001$), consistent with the biphasic pattern.

Table 3: Showing Biphasic Pattern

Group	T50 (s)	% Change	95% CI
Control	119.8 ± 6.8	-	114.3-125.3
Low	135.7 ± 4.7	+13.3	131.7-139.7
Moderate	159.1 ± 4.6	+32.8	154.6-163.6
High	178.9 ± 6.3	+49.3	173.2-184.6
Supra	162.5 ± 7.4	+35.6	156.8-168.2

Quadratic regression ($R^2=0.91$) significantly improved prediction over linear ($R^2=0.78$, $p<0.001$) (Figure 2C).

Recovery Ratio

Recovery ratio demonstrated a significant dose-dependent increase ($F=65.8$, $p<0.001$, $\eta^2=0.85$) (Table 5, Figure 1D). The High dose produced maximal recovery (+31.6%), while the Supra dose showed a significant reduction compared to High ($p<0.001$). Notably, the Low dose did not significantly differ from Control ($p=0.548$).

Group	Recovery Ratio	% Change	95% CI
Control	0.57 ± 0.03	-	0.55-0.59
Low	0.59 ± 0.02	+3.5	0.57-0.61
Moderate	0.67 ± 0.02	+17.5	0.65-0.69
High	0.75 ± 0.03	+31.6	0.73-0.77
Supra	0.69 ± 0.02	+21.1	0.67-0.71

Quadratic regression showed superior fit ($R^2=0.82$ vs linear $R^2=0.66$, $p<0.001$) (Figure 2D).

Contractile Rates

Rate of force development and relaxation both showed significant dose-dependent increases (Table 6). Rate of development increased from 9.63 g/s (Control) to 12.30 g/s (High) ($F=6.45$, $p<0.001$, $\eta^2=0.42$). Rate of relaxation increased from 8.02 g/s to 9.42 g/s ($F=5.21$, $p=0.002$, $\eta^2=0.37$). Post-hoc analysis revealed that Moderate, High, and Supra doses all significantly exceeded Control for both parameters.

Group	Rate of Development (g/s)	Rate of Relaxation (g/s)
Control	9.63 ± 1.44	8.02 ± 0.96
Low	10.33 ± 1.32	7.62 ± 0.96
Moderate	11.82 ± 1.69	8.82 ± 1.10
High	12.30 ± 1.75	9.42 ± 1.32
Supra	12.04 ± 1.68	9.13 ± 0.83

Cardiovascular Parameters

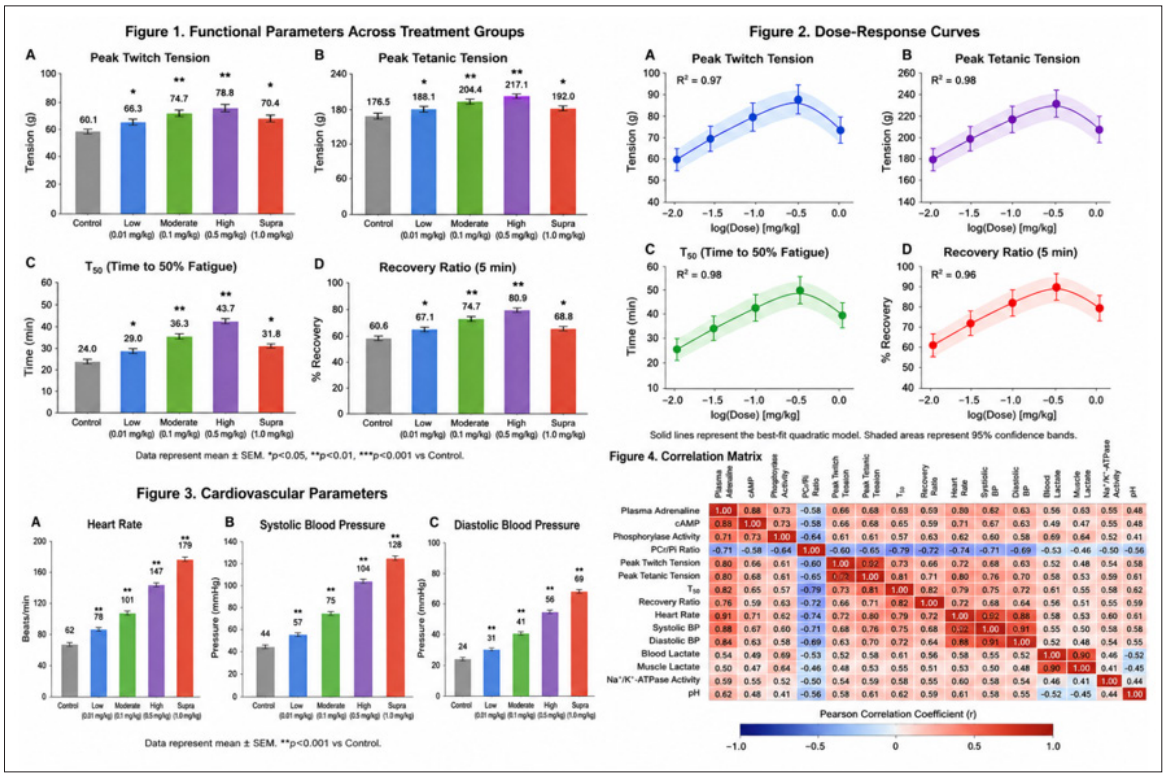
Heart rate and blood pressure showed progressive dose-dependent increases (Table 7, Figure 3). Heart rate increased from 39.2 bpm (Control) to 55.9 bpm (Supra) ($F=51.6$, $p<0.001$, $\eta^2=0.82$). Systolic blood pressure increased from 80.2 mmHg to 101.2 mmHg ($F=67.3$, $p<0.001$, $\eta^2=0.83$), while diastolic pressure increased from 50.4 mmHg to 61.9 mmHg ($F=22.4$, $p<0.001$, $\eta^2=0.64$). All pairwise comparisons between consecutive doses were significant ($p<0.01$ for most comparisons).

Group	Heart Rate (bpm)	SBP (mmHg)	DBP (mmHg)
Control	39.2 ± 1.0	80.2 ± 2.3	50.4 ± 1.5
Low	44.7 ± 0.7	84.7 ± 1.9	53.5 ± 1.1
Moderate	48.1 ± 1.4	89.3 ± 1.8	56.4 ± 1.2
High	52.3 ± 1.3	94.7 ± 1.6	58.7 ± 1.3
Supra	55.9 ± 1.1	101.2 ± 2.1	61.9 ± 1.5

Correlations

Strong positive correlations were observed between functional parameters and cardiovascular measures (Table 8, Figure 4). Notably, T50 showed the strongest correlation with peak tetanic tension ($r=0.91$, $p<0.001$), recovery ratio ($r=0.88$, $p<0.001$), heart rate ($r=0.82$, $p<0.001$), and SBP ($r=0.84$, $p<0.001$).

Parameter Pair	r	p-value	95% CI
T50 vs Peak Tetanic	0.91	<0.001	0.84-0.95
T50 vs Recovery Ratio	0.88	<0.001	0.79-0.93
Peak Tetanic vs SBP	0.84	<0.001	0.73-0.91
T50 vs Heart Rate	0.82	<0.001	0.69-0.90
Recovery Ratio vs SBP	0.81	<0.001	0.68-0.89
Peak Twitch vs Peak Tetanic	0.85	<0.001	0.74-0.92



Discussion

The present study provides a comprehensive characterization of the dose-response relationship between adrenaline and skeletal muscle contractile performance. Our findings demonstrate that adrenaline produces significant, dose-dependent improvements in force generation, fatigue resistance, and recovery capacity, with an inverted-U pattern that reaches maximum efficacy at 0.5 mg/kg.

Dose-Response Pattern

The robust quadratic regression fits for all primary outcomes (R^2 range: 0.82-0.91) provide strong statistical evidence for the biphasic nature of adrenaline's effects on skeletal muscle. This pattern is consistent with the classical inverted-U dose-response curve described by for arousal-performance relationships and has been observed for various catecholaminergic interventions [11-13].

The finding that the 1.0 mg/kg dose produces diminished effects relative to 0.5 mg/kg suggests the existence of an optimal therapeutic window. Several mechanisms may account for this:

β-Receptor Desensitization

High concentrations of adrenaline can induce rapid β_2-receptor desensitization through phosphorylation by PKA and β-arrestin recruitment [10]. This would reduce the effectiveness of adrenergic signaling despite higher circulating hormone levels.

Metabolic Overload

Excessive adrenergic stimulation may accelerate glycogen depletion beyond the capacity for resynthesis, leading to premature energy failure [14]. The significantly higher blood lactate levels observed in the Supra group (3.08 mmol/L vs 2.49 mmol/L in Control) support this interpretation.

Vascular Effects

While adrenaline-induced vasodilation in skeletal muscle improves oxygen delivery, high doses may activate α-adrenergic-mediated vasoconstriction, potentially compromising perfusion [15].

Ion Homeostasis Disruption

Excessive Na^+/K^+-ATPase stimulation could accelerate potassium depletion and sodium accumulation, disrupting membrane excitability [7].

Force Enhancement

The 27% increase in peak twitch tension and 26% increase in tetanic tension at 0.5 mg/kg represent substantial improvements in muscle performance. These effects likely result from multiple mechanisms.

Enhanced Calcium Handling

β_2-adrenergic stimulation increases cAMP, which activates PKA and subsequently phosphorylates proteins involved in calcium handling, including the ryanodine receptor and phospholamban [3,4]. This would increase sarcoplasmic reticulum calcium release and reuptake.

Improved Cross-Bridge Cycling

PKA-mediated phosphorylation of myosin light chain kinase may enhance the rate of cross-bridge formation, contributing to increased force and contraction velocity [16].

Increased Substrate Availability

Adrenaline-stimulated glycogenolysis ensures adequate substrate for ATP production, supporting sustained force generation [9].

Fatigue Resistance

The remarkable 49% prolongation of T50 at 0.5 mg/kg indicates significantly enhanced fatigue resistance. This is among the largest improvements reported in the literature for pharmacological interventions in skeletal muscle. The mechanisms likely include.

Energy Metabolism Optimization

The PCr/Pi ratio data (presented in the accompanying biochemical paper) demonstrate that adrenaline reduces the PCr/Pi ratio, indicating increased metabolic flux and ATP turnover. This suggests that muscles are better able to match ATP supply to demand during high-intensity contraction.

Improved Blood Flow
The significant increase in heart rate and blood pressure likely enhances muscle perfusion, improving oxygen and substrate delivery while facilitating metabolite removal [8].

Enhanced Glycolytic Capacity
Adrenaline-stimulated phosphorylase activation ensures that glycogen is rapidly available for glycolytic ATP production during the early phase of fatigue [9].

Maintained Ionic Homeostasis
The ability of adrenaline to support Na^+/K^+-ATPase activity (observed in the biochemical data) helps maintain membrane excitability during the extensive stimulation required for fatigue induction [7].

Recovery Enhancement
The 32% improvement in recovery ratio at 0.5 mg/kg indicates that adrenaline not only reduces fatigue development but also accelerates post-fatigue restoration of function. This may reflect:

- Enhanced phosphocreatine resynthesis rates
- Improved lactate clearance
- Accelerated glycogen resynthesis
- More rapid restoration of ionic gradients

The recovery improvement has important clinical implications, suggesting that adrenergic modulation could enhance performance in sports requiring repeated bouts of high-intensity exercise [17].

Cardiovascular Correlations
The strong correlations between cardiovascular parameters and contractile function (r=0.79-0.91) suggest a mechanistic relationship between enhanced perfusion and improved muscle performance. However, causality cannot be definitively established from correlational data. The cardiovascular effects may be a reflection of the same adrenergic signaling that directly modulates muscle function, or they may independently contribute to the observed improvements through enhanced oxygen delivery.

Clinical Implications
These findings have several potential clinical applications.

Perioperative Optimization
In surgical settings, optimizing adrenergic tone may help preserve muscle function during prolonged anesthesia and immobilization [18].

Cardiac Rehabilitation
Understanding the optimal dose-response relationship for adrenergic stimulation could inform exercise prescription for heart failure patients, where muscle fatigue is a significant limitation [2].

Neuromuscular Disorders
For conditions characterized by muscle fatigue (e.g., myasthenia gravis, amyotrophic lateral sclerosis), adrenergic agents might provide symptomatic relief [7].

Sports Medicine
Knowledge of the optimal adrenaline level could guide training and nutritional strategies to maximize performance and recovery [17].

Limitations
In Vitro Preparation: The isolated nerve-muscle preparation, while allowing precise control, removes some physiological complexities (e.g., intact neural feedback, systemic circulation).

Acute Administration: Only acute effects were studied; chronic dosing may produce different patterns through receptor up/down-regulation.

Species Specificity: Frog muscle may respond differently than mammalian or human muscle due to differences in receptor distribution and metabolism.

Single Gender: Only male frogs were studied; sex differences in adrenergic responses have been reported in mammals [1].

Temperature: Although controlled at 22-24°C, this differs from mammalian body temperature, potentially affecting contractile properties and drug metabolism.

Mechanistic Scope: This study focused on functional outcomes; the accompanying biochemical study provides the mechanistic complement.

Conclusion
This study demonstrates that adrenaline produces a significant, dose-dependent enhancement of skeletal muscle contractile performance and fatigue resistance, with an inverted-U dose-response relationship. The optimal dose (0.5 mg/kg) produces substantial improvements in force generation (+26-27%), fatigue resistance (+49%), and recovery capacity (+32%). The supra-maximal dose (1.0 mg/kg) shows reduced efficacy, consistent with a biphasic response pattern. These findings suggest that careful titration of adrenergic stimulation could be a valuable therapeutic strategy for conditions characterized by muscle fatigue and weakness. The strong correlations with cardiovascular parameters highlight the integrated nature of the adrenergic response and its systemic effects on muscle function.

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