Influence of Acute Melatonin Administration on Human Physical Performance: A Systematic Review

Vinícius Silva Faria, MSc,[†] Leonardo Henrique Dalcheco Messias, MSc, PhD,[‡] Taciane Maria Melges Pejon, MSc,[†] and Wladimir Rafael Beck, MSc, PhD*[†]

Context: Melatonin is an ancient molecule with a wide range of functions in mammals, such as antioxidant, anti-inflammatory, and hypothermic effects among others. However, the influence of acute melatonin administration on human physical performance is debatable.

Objective: To summarize available data from controlled trials about the effects of acute melatonin administration on human physical performance, especially with respect to strength, power, speed, and short- and long-term continuous exercise.

Data Sources: A systematic search of the PubMed, Web of Science, Scopus, Embase, and Cochrane databases up to December 10, 2021, was conducted using specified keywords and Boolean operators ("melatonin" AND "exercise OR circuit-based exercise OR plyometric exercise OR exercise tolerance OR exercise test").

Study Selection: Only controlled studies in the English language and with humans were accepted.

Study Design: Systematic review.

Level of Evidence: Level 1.

Data Extraction: Participants' characteristics (sex, age, body mass, height and fat percentage), melatonin dose and administration time, and outcomes from the performance trial were extracted.

Results: A total of 10 studies were identified after the screening process. Overall, melatonin did not change speed or short-term continuous exercise performances. However, in relation to strength and power, the results are debatable since 5 articles showed no difference, while another 2 pointed to a decrease in performance. In terms of performance improvement, only 1 study reported an increase in balance and another in long-term continuous exercise performance in nonathletes, with no advantage found for athletes.

Conclusion: Melatonin did not cause any significant change in strength, speed, power, and short-term continuous exercise performances. In fact, it led to reduced strength and power performances in specific tests. On the other hand, melatonin seems to have improved balance and long-term continuous exercise performance, at least in nonathletes. More investigations are required to corroborate these findings.

Keywords: long-term continuous exercise; melatonin; power; short-term continuous exercise; strength

Melatonin (N-acetyl-5-methoxytryptamine) is an ancient molecule present in almost all living organisms. In mammals, although it is synthesized mainly by pinealocytes and released into the blood, melatonin is also found in several extra pineal tissues, such as the brain, retina, liver, and skeletal muscle among others.[2] Since the discovery of melatonin production from the pineal gland by Lerner et al,[31] this indoleamine has been associated with a wide range of

From [†]Laboratory of Endocrine Physiology and Physical Exercise, Department of Physiological Sciences, Federal University of São Carlos, São Carlos, SP, Brazil, and [‡]Research Group on Technology Applied to Exercise Physiology - GTAFE, Health Sciences Postgraduate Program, São Francisco University, Bragança Paulista, SP, Brazil
*Address correspondence to Wladimir Rafael Beck, MSc, PhD, Laboratory of Endocrine Physiology and Physical Exercise, Department of Physiological Sciences, Federal University of São Carlos - Washington Luis, Km 235., São Carlos, São Paulo, Brazil (email: beckwr@ufscar.br).
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Table 1. Eligibility criteria based on the PICOS framework

Component	Feature
Population	Healthy subjects, including athletes and nonathletes
Intervention	Physical test with 1 melatonin administration before trial
Comparator	Physical test without melatonin administration
Outcomes	Strength, speed, power, and short-term and long-term continuous exercise
Study design	Controlled trials

PICOS, Population, Intervention, Comparator, Outcomes, and Study Design.

functions, including the control of circadian and seasonal rhythms,[11,25,44,47] antioxidant and anti-inflammatory effects,[12,22,30,35,36,42,46,48] and energy metabolism homeostasis.[14]

Regarding the bioavailability and pharmacokinetics of exogenous melatonin administration, this hormone is absorbed rapidly and reaches maximal plasma concentration at between approximately 30 and 45 minutes after oral ingestion,[3] with a half-life of about 45 minutes.[26] The dosage range used varies from 0.1 to 300 mg per day for long-term administration and up to 2000 mg for short-term administration.[28,51,55] In addition, even though exogenous melatonin toxicology and safety have been studied in a limited manner, the general conclusion is that melatonin lacks toxic adverse effects and is a safe drug for clinical treatments.[15]

Compelling evidence has demonstrated the association of melatonin with a depressive effect on the central nervous system,[10,41] reduced alertness,[4,21,32,52] and decreased body temperature.[4,17,24,27,54] Regarding the latter, strategies to reduce initial body temperature before exercise, or attenuate the rate of heat gain during exercise can increase the time needed to reach a critical limiting temperature, thus prolonging exercise performance.[50] In addition to the hypothesis about the relationship between reduced body temperature and physical exercise performance, other studies have demonstrated a superior performance in balance and long-term continuous exercise tests in humans and rats acutely treated with different doses of melatonin, such as 6 mg, 10 mg, and 10 mg/kg.[5,6,7,18,29] Despite the apparent association between melatonin and physical performance, other studies did not observe a positive result.[4,10,19,20,23,24,37,43] The debate could be anchored in different demands from a wide range of physical exercise features, since power and strength performances are expected to depend on different physiological aspects of long-term continuous exercise. Therefore, the physiological effects of acute melatonin administration could be advantageous for certain types but not necessarily all exercise performance. Nevertheless, the current literature does not clearly elucidate whether there is an effect of acute administration of this indoleamine on some parameters related to physical performance. For this reason, in this review, we systematically summarized available data from controlled trials about the effects of acute melatonin administration on human physical performance, especially with respect to strength, power, speed, and short- and long-term continuous exercise.

METHODS

Search Strategy

A search was conducted on the PubMed, Web of Science, Scopus, Embase, and Cochrane databases up to December 10, 2021. Boolean operators were used in various combinations as primary search words, such as "melatonin" AND "exercise OR circuit-based exercise OR plyometric exercise OR exercise tolerance OR exercise test." The filters for "controlled studies," "studies in English," and "humans" were activated. In addition, a manual search of reference lists of included and nonincluded studies was performed.

Eligibility Criteria

The Population, Intervention, Comparator, Outcomes, and Study Design (PICOS) framework was adopted for eligibility criteria (Table 1).[1] The screening of studies was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[39] Studies were considered without restriction of publication date. Original articles were included if (1) only 1 melatonin administration was provided before the performance trial (acute effect); (2) the time of day of melatonin administration was specified; (3) the melatonin dose was properly described; and (4) the performance trial was shown, along with the outcomes of interest. Concerning outcomes related to physical performance, any result associated with strength, speed, power, and short- and long-term continuous exercise was considered. Studies were excluded if (1) they evaluated only the effect of exercise on melatonin secretion; (2) chronic supplementation of melatonin was conducted; (3) melatonin was administered before sleep and the performance test was conducted on the next day; (4) studies were performed with animals; and (5) they comprised only abstracts, without full texts. It is important to mention that we contacted the corresponding authors of the articles not found in full text and received no response.

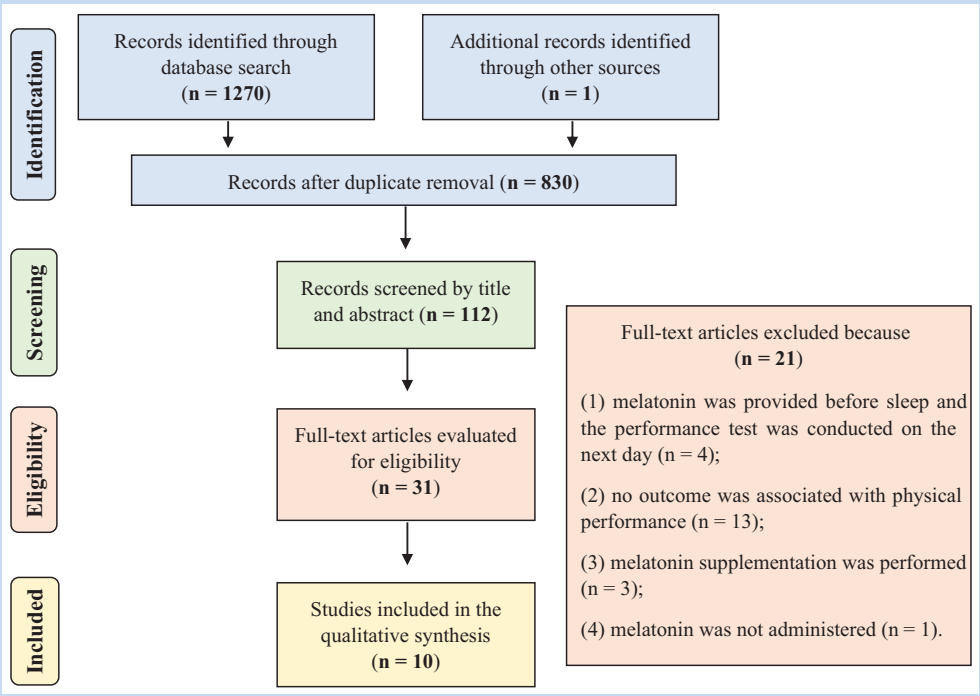

Figure 1. Flow diagram of the study selection using PRISMA guidelines. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Data Extraction

The titles of studies retrieved from the databases were inserted in Microsoft Excel sheets. Two researchers independently screened the manuscripts by title, abstract, and full text. Any discrepancies were checked by a 3rd reviewer to resolve disagreement. Participant characteristics (ie, sex, age, body mass, height, and fat percentage), melatonin dose and administration time, and outcomes from the performance trial were extracted from the included studies.

Quality Assessment of Individual Studies

Two reviewers independently performed quality analysis using the Physiotherapy Evidence Database (PEDro) scale.[33] This instrument consists of 11 items that yield 1 point - except the first item - to the final score. The final assessments varied from fair-to-substantial to fair-to-good.

RESULTS

Literature Search and Quality Assessment

The initial literature search identified 1270 studies (Figure 1). Based on the first search, 440 duplicates were identified. After screening by title, abstract, and full text, 10 studies met the eligibility criteria (Table 2).[4,6,10,19,20,23,24,29,37,43] The included studies were published between the years 2005 and 2021 and conducted in 6 countries: the United Kingdom,[4] Finland,[37] Tunisia,[19,20,23,24] the United States,[10] Brazil,[6] and Iran.[29,43] The mean and standard deviation of the PEDro score among the studies was 9.80 ± 0.42. Of the 10 studies, 8 were classified with a score of 10 and 2 with a score of 9.

Study and Participant Characteristics

A total of 115 healthy participants participated in the randomized controlled trials with acute melatonin administration. The mean and standard deviation of age (21.40 ± 3.37 years), body mass (73.57 ± 7.03 kg), height (1.77 ± 0.02 m), and fat % (13.02 ± 2.98%) of the participants were calculated from available data. The average sample size was 11 ± 1, with a minimum of 10 and a maximum of 15 people per study; 3 studies examined adolescents,[19,20,24] whereas the other 7 evaluated only adults (people aged >18 years),[4,6,10,23,29,37,43] of which 6 were performed with men (n = 63),[4,6,10,29,37,43] 1 exclusively with women (n = 15),[20] and 3 did not clearly report the sex of the participants (n = 37).[19,23,24] All participants were considered trained, except in 1 study, in which they were considered moderately active.[6]

Concerning the outcomes, the studies evaluated the performance of melatonin-treated participants in strength and balance[4,23,24,29,37,43]; speed, velocity, and agility[20,23,24]; power[4,10,20,23,24,29,37,43]; and short- and long-term continuous exercise tests.[4,6,10,19]

Time of Day and Dose of Melatonin Administration

The most frequently used doses were 6 mg,[6,19,20,37,43] and 5 mg,[4,10,23,24] found in 45% and 36% of the studies, respectively,

Table 2. Overview of the included studies. Values for age, BM, HT, and fat percentage are expressed as mean ± SD

Study	Training Status and Gender	Age, BM, HT, and Fat Percentage	Melatonin Dose	Administration Time	Performance Tests	Difference (*P* Value)[a]	Outcomes
Atkinson et al[4]	Trained men (n = 12)	Age, 25 ± 5 years BM, 81.4 ± 12.1 kg HT, NP Fat %, NP	5 mg (Penn Pharmaceuticals)	11:45 am	- 4-km cycling time; - Left and right grip strength	↔ ($P > 0.05$) ↔ ($P > 0.05$)	Short-term continuous exercise and strength
Mero et al[37]	Trained men (n = 10)	Age, 24 ± 3 years; BM, 74.7 ± 5.4 kg HT, 1.78 ± 0.05 m Fat %, 14.3 ± 3.4	6 mg (University Pharmacy)	10:00-11:00 am	- Resistance exercise session (15 × 5 RM + 10 × 10 RM; ~80 min); - Countermovement jump; - 1 RM (bench press and deep squat)	↔ ($P > 0.05$) ↔ ($P > 0.05$) ↔ ($P > 0.05$)	Strength and power
Ghattassi et al[23]	Trained (NP) (n = 12)	Age, 22 ± 1 years BM, 72.0 ± 8.8 kg HT, 1.80 ± 0.05 m Fat %, NP	5 or 8 mg (Jamieson Laboratories)	09:00 pm	- Squat jump; - Countermovement jump; - Medicine ball throw; - 5-jump test; - Handgrip strength; - Agility tests	↓* ($P < 0.001$) ↓[b] ($P < 0.001$) ↔ ($P > 0.05$) ↔ ($P > 0.05$) ↓ ($P < 0.01$) ↔ ($P > 0.05$)	Strength, speed, and power
Ghattassi et al[24]	Trained (NP) (n = 12)	Age, 17 ± 1 years BM, 62 ± 8 kg HT, 1.74 ± 0.06 m Fat %, NP	5 mg (Jamieson Laboratories)	07:30 am	- Medicine ball throw; - 5-jump test; - Handgrip strength; - Modified agility T-test.	↓ ($P < 0.05$) ↔ ($P > 0.05$) ↓ ($P < 0.05$) ↔ ($P > 0.05$)	Strength, speed, and power
Brandenberger et al[10]	Trained men (n = 10)	Age, 25 ± 4 years BM, 69.9 ± 9.1 kg HT, 1.76 ± 0.07 m Fat %, 9.2 ± 3.2	5 mg (NP)	02:00-06:00 pm	- 32.2-km cycling time trial	↔ ($P > 0.05$)	Long-term continuous exercise
Beck et al[6]	Moderately active men (n = 11)	Age, 24 ± 3 years BM, 87.0 ± 12.4 kg HT, 1.82 ± 0.05 m Fat %, 16.2 ± 5.7	6 mg (Optimum Nutrition, Inc)	06:00-09:00 pm	- Time to exhaustion test	↑ ($P = 0.03$)	Long-term continuous exercise

(continued)

Table 2. (continued)

Study	Training Status and Gender	Age, BM, HT, and Fat Percentage	Melatonin Dose	Administration Time	Performance Tests	Difference (*P* Value)[a]	Outcomes
Farjallah et al[20]	Trained women (n = 15)	Age, 17 ± 0 years BM, 76.4 ± 5.6 kg HT, 1.76 ± 0.04 m Fat %, NP	6 mg (Jamieson Laboratories)	04:00-04:30 pm	- Modified agility *T*-test; - Squat jump; - Counter movement jump; - Maximum standing ball throw velocity test; - Maximum jump ball throw velocity test; - 20-m sprint.	↔ (*P* > 0.05) ↔ (*P* > 0.05) ↔ (*P* > 0.05) ↔ (*P* > 0.05) ↔ (*P* > 0.05) ↔ (*P* > 0.05)	Strength, speed, and power
Khaleghi-Mamaghani et al[29]	Trained men (n = 10)	Age, 23 ± 1 years BM, 74.2 ± 6.69 kg HT, 1.76 ± 0.06 m Fat %, 13.4 ± 2.75	10 mg (NP)	11:00 am	- Static and dynamic balance; - Jump strength test; - Upper body, lower body, handgrip, and strength (bench press, squat, and Saehan digital hand dynamometer); - Running-based anaerobic sprint test.	↑ (*P* = 0.003) ↔ (*P* = 0.89) ↔ (*P* = 0.89; *P* ≥ 0.99; *P* = 0.27) ↔ (*P* > 0.05)	Strength and power
Paryab et al[43]	Trained men (n = 10)	Age, 20 ± 2 years BM, 67.8 ± 12.4 kg HT, 1.75 ± 0.01 m Fat %, NP	6 mg (NP)	08:00 am	- Static and dynamic balance; - Wingate anaerobic test.	↔ (*P* > 0.05) ↔ (*P* > 0.05)	Strength and power
Farjallah et al[19]	Trained (NP) (n = 13)	Age, 17 ± 1 years BM, 70.3 ± 3.9 kg HT, 1.80 ± 0.08 m Fat %, NP	6 mg (Jamieson Laboratories)	05:00 pm-00:30 am	- Running exercise test	↔ (*P* = 0.19)	Short-term continuous exercise

BM, body mass; HT, height; NP, not presented; RM, repetition maximum. Values for age, BM, HT, and fat percentage are expressed as mean ± SD.
[a]↓ Melatonin condition reduced performance in this variable compared with placebo condition; ↔ melatonin condition was not different from placebo condition for this variable; ↑ melatonin condition improved performance in this variable compared with placebo condition.
[b]Difference between melatonin and placebo conditions only when 8 mg of hormone was administered.

while doses of 8 and 10 mg were used each in only 9% of the studies.[23,29] Furthermore, 5 studies administered the indoleamine in the morning (between 12:00 am and 12:00 pm),[4,23,29,37,43] 3 in the afternoon (between 12:00 pm and 6:00 pm),[10,19,20] and 3 in the evening (between 6:00 pm and 12:00 am).[6,23,19] The majority of studies administered melatonin between 30 and 60 minutes before the physical performance test.[6,19,20,23,24,29,37,43] Melatonin administration was performed for less than 30 minutes in only 1 study,[10] and for more than 60 minutes in 2 studies.[4,24]

Strength and Balance

Of the 10 included studies, 5 measured maximal isometric strength through the handgrip strength and static balance tests,[4,23,24,29,43] while 3 assessed isotonic strength through 1-repetition maximum (RM) and dynamic balance tests.[29,37,43] Of the included studies, 2 demonstrated a decrease in handgrip performance,[23,24] whereas 1 demonstrated an enhanced static and dynamic balance in participants treated with melatonin.[29] On the other hand, no difference was found between participants who received an acute dose of melatonin or placebo for the handgrip,[4,29] and static and dynamic balance tests.[43] In addition, 1 study analyzed force resistance during a resistance exercise session, which was designed to be a high-volume session consisting of a total of 25 sets (15 × 5 RM + 10 × 5 RM), with a large amount of muscle mass being recruited and activated. In this study, the loading volume (kg × repetitions × sets) did not change after melatonin administration.[37]

Speed, Velocity, and Agility

Three studies assessed speed with direction changes through agility tests, and no difference between melatonin and placebo conditions was observed.[20,23,24] However, according to Ghattassi et al,[24] melatonin-treated participants showed a better performance in the late hours than in the early hours of the day (04:00 pm in relation to 12:00 pm and 08:00 am).

Power

In all, 80% of the studies assessed physical power using a variety of tests. Nonetheless, the results of the squat jump, countermovement jump, and medicine ball throw tests revealed a reduced power performance in melatonin-treated participants,[23,24] while the remaining studies indicated no significant change between people treated with melatonin and placebo.[20,23,24,29,37,43]

Short- and Long-Term Continuous Exercise

Four studies analyzed physical performance in cycle ergometers or running exercise tests.[4,6,10,19] Only Beck et al[6] demonstrated an improvement in long-term continuous exercise performance in nonathletes treated with melatonin, whereas the other 3 showed no difference between melatonin and placebo treatments.[4,10,19]

DISCUSSION

To the best of our knowledge, this is the first review that has systematically summarized the effects of acute melatonin administration on human physical performance. Results from only 2 studies showed that exogenous melatonin administration reduced the performance of athletes submitted to melatonin treatment in specific strength and power tests, while no change was observed in speed and short-term continuous exercise tests. In contrast, 2 studies reported an increased performance in balance and long-term continuous exercise in participants treated acutely with melatonin.[6,29]

Two studies investigated the effects of morning and nocturnal melatonin ingestion on physical performance.[23,24] Regarding the first administration period, strength (handgrip test) and power (squat jump and countermovement jump tests) were reduced only when the participants were treated with 8 mg of melatonin.[23] In a similar study, Ghattassi et al[24] also demonstrated that 5 mg of melatonin was responsible for reducing strength (handgrip test) and power (medicine ball throw test) performances. Conversely, Khaleghi-Mamaghani et al[29] indicated an improvement in balance performance in participants treated with melatonin (10 mg) (pre- vs post-test), whereas in the placebo condition no difference was found. The remaining studies did not show any significant change in strength or power in melatonin-treated participants.[4,10,20,23,24,29,37,43] The results then suggest that melatonin does not increase strength and power, but may instead reduce them in some cases. Intriguingly, 2 studies investigating the impact of melatonin on balance provided opposite conclusions: while 1 study reported an increase in balance performance, the other showed no difference between static and dynamic balance.[43] Furthermore, there was no difference in speed between participants treated with melatonin and placebo.[20,23,24]

The literature suggests that a better short-duration maximal exercise performance (ie, continuous and intermittent exercises or very brief all-out efforts, such as the Wingate test, the repeated sprint ability test, maximal jumps, or isometric contractions) is achieved in the late afternoon and in the early evening (4:00 pm-8:00 pm) than in the morning in both dynamic and isometric exercise modes.[13,38] In parallel, body temperature achieves the daily peak value in the evening (6:00 pm),[53] which has been suggested to affect the contractile properties, viscosity, and conduction velocity of action potentials in the skeletal muscle.[13] In fact, Racinais and Oksa[45] demonstrated an improvement in performance from 2% to 5% with a 1°C increase in muscle temperature. In contrast, Bergh and Ekblom[8] showed that power output decreased by 5% for every 1°C decrease in muscle temperature in warming and cooling experiments at muscle temperatures between 30°C and 39°C. In this context, the literature has demonstrated the ability of melatonin to affect body temperature, reducing it by approximately 0.10°C to 0.49°C.[4,17,27,54] Such evidence indicates

that the reduction in strength and power performance could be associated, at least partially, with the ability of melatonin to decrease body temperature and alertness.

Regarding continuous physical exercise, 2 studies evaluated physical performance in short-term continuous exercise.[4,19] Atkinson et al[4] selected 12 physically active men who were treated with melatonin (5 mg) or placebo during the morning (11:45 am) and then submitted to a 4-km cycling time trial after 1 hour and 15 minutes (1:00 pm) and after 5 hours and 15 minutes (05:00 pm). In both cases, no difference between melatonin (1:00 pm, 398 ± 53 seconds; 5:00 pm, 405 ± 59 seconds) and placebo treatments (1:00 pm, 389 ± 46 seconds; 5:00 pm, 403 ± 52 seconds) was found. According to the authors, the lack of performance improvement is related to the hypothermic effects of melatonin, which cause different effects on endurance and short-term exercise performance. In endurance exercise in the heat, a lower pre-exercise body temperature may delay the time needed to reach high body temperature,[4] being an advantage in such situations, but not for short-term continuous exercise. Farjallah et al[19] recruited 13 professional soccer players who received a quick-release capsule of vegetable melatonin (6 mg) or placebo in the evening (5:00 pm- 00:30 am) followed by submission after 30 minutes to running exercise to exhaustion. No time duration difference between melatonin (374.54 ± 57.97 seconds) and placebo (362.46 ± 42.02 seconds) conditions was observed. The authors suggested that melatonin was not ergogenic because of the proposed exercise model (running) and the duration (short), in addition to the time of day (afternoon) and dose (6 mg) of melatonin administered.

With regard to long-term continuous exercise, 2 studies provided opposite conclusions: whereas 1 reported performance improvement in nonathletes,[5] the other observed no performance increase in athletes.[10] Brandenberger et al[10] recruited 10 male endurance-trained cyclists and treated them with a tablet of 5 mg of melatonin or a multivitamin (considered as a placebo condition by the authors). After 15 minutes, the cyclists were submitted to a 32.2-km cycling time trial; no change between both conditions was observed (melatonin, 64.94 ± 5.95 minutes; placebo, 65.26 ± 6.85 minutes). Conversely, Beck et al[6] selected 11 moderately active men and submitted them to a time-to-exhaustion test at a lactate anaerobic threshold determined individually under 2 conditions: melatonin (6 mg) and placebo ingestion sessions, which took place 30 minutes before the performance test. The time to exhaustion was longer with melatonin (41.94 ± 17.22 minutes) than with placebo (33.94 ± 15.26 minutes) treatment. Although the results are conflicting, according to Beck et al,[6] melatonin may have positively influenced performance in continuous long-term exercise because of its ability to reduce catecholamine levels, body temperature (hypothermic effect), and alertness - although such parameters were not systematically measured in that study.

Compelling evidence has demonstrated the effectiveness of cooling strategies to reduce initial body temperature before exercise (precooling), or attenuate the rate of heat gain during exercise (percooling). Such strategies have been shown to increase the time required to reach a critical limiting temperature, thus prolonging exercise performance.[9,40,50] In addition to the well-known precooling methods, ie, external (cold air exposure, water exposure, and exposure to ice or ice-products), internal (air inhalation, beverage ingestion, and ice ingestion), and combined precooling strategies,[16,34,49,50] melatonin has demonstrated a relevant hypothermic effect,[4,17,27,54] which is considered a key factor for improving continuous long-term exercise performance. However, the benefits of precooling are greater for endurance athletes than for (intermittent) sprint athletes, since sprint exercise is influenced mainly by muscle temperature and anaerobic metabolism rather than thermoregulatory factors. On the other hand, endurance exercise (moderate- to high-intensity) results in a greater thermoregulatory burden than sprint exercise.[9] Therefore, although conflicting, the results suggest that melatonin has potentially positive effects on long-term continuous exercise in nonathletes. Further studies are therefore necessary to better understand the mechanisms of action of melatonin on human physical performance.

This systematic review must be interpreted in light of its limitations. Among the limitations are the reduced number of studies focusing on the effects of acute melatonin administration on human physical performance, mainly in relation to continuous long-term exercise, on which melatonin could have a positive influence; the lack of information about the origin of melatonin (company or laboratory), and the exact time of administration, which are relevant for studies that use this indoleamine; the lack of information about the participants' characteristics and the small sample size; the poor description of the proposed exercise; and the numerical values of the results.

The outcomes of this study could be useful for those engaged in long-term continuous exercise; however, it is important to consider the dose and time of melatonin administration before exercise. In addition, although the results are conflicting, the literature suggests administration of 6 mg of melatonin 30 to 45 minutes before long-term continuous exercise to improve performance.[6] Nevertheless, other concentrations of melatonin should be tested to achieve a similar effect with a lower dose. Moreover, special attention should be paid to the time of day the indoleamine is administered, given its important role in circadian and seasonal rhythms. Therefore, this study is relevant, as it highlights the state of the art on the effects of melatonin on physical performance to date, in addition to stimulating new research on the effect of melatonin on long-term physical exercise, on which the hormone apparently has a positive influence.

Overall, melatonin was not able to improve the participants' strength, power, speed, and short-term continuous exercise performance. Particularly in relation to the first 2 variables, melatonin led to reduced performance in specific strength and power tests. Only 2 studies demonstrated an improvement in balance and long-term continuous exercise performance in nonathletes. However, the variety of tests, doses, and times of

administration prevented strong conclusions about the adoption of acute melatonin ingestion as a possible ergogenic agent.

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ORCID ID

Wladimir Rafael Beck https://orcid.org/0000-0001-7176-2713

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