Acute effects of heavy resistance exercise on biomarkers of neuroendocrine-immune regulation in healthy adults: a systematic review

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ABSTRACT

Background: The nervous system integrates the immune system in the systemic effort to maintain or restore the organism's homeostasis. Acute bouts of exercise may alter the activity of specific pathways associated with neuroendocrine regulation of the immune system.
Objective: To examine the acute effects of heavy resistance exercise on biomarkers of neuroendocrine-immune regulation in healthy adults.
Methods: A systematic literature search was conducted using PubMed, Cochrane Controlled Trials Register, Web of Science and SportDiscus with no date restrictions up to March 2021. Clinical trials in English or German were included if they measured the blood plasma or serum concentrations of specific biomarkers of neuroendocrine-immune regulation (adrenaline, noradrenaline, acetylcholine, vasoactive intestinal peptide (VIP), cortisol, growth hormone, calcitonin gene-related peptide (CGRP), substance p, serotonin, brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) or glia-derived neurotrophic factor (GDNF)) in a resting state prior to and no later than 60 minutes after an acute bout of heavy resistance exercise in healthy adults.
Results: 7801 records were identified through literature search, of which 36 studies, with a total of 58 intervention groups, met the inclusion criteria. Evidence was found that an acute bout of heavy resistance exercise increased the levels of adrenaline (median: 185%), noradrenaline (median: 113%) and GH (median: 265%) immediately after the exercise. Mixed results were found for cortisol (median: 0%), suggesting that its response might be more sensitive to the configuration of the exercise scheme. The limited evidence regarding the effects on BDNF and ACTH allows no firm conclusions to be drawn about their response to heavy resistance exercise. The vast majority of the included studies reported a return of the biomarker concentrations to their baseline value within one hour after the termination of the exercise bout. No studies were identified that investigated the response of acetylcholine, VIP, CGRP, substance p, serotonin, NGF or GDNF to heavy resistance exercise.
Conclusions: A bout of heavy resistance exercise alters the circulating concentrations of selected biomarkers of neuroendocrine-immune regulation. Both subject characteristics, such as sex as well as exercise parameters, such as rest intervals appear to have the potential to influence these effects.

Keywords: Resistance exercise; nervous system; immune system; neuroendocrine reaction; immune regulation

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INTRODUCTION

The nervous system and the immune system are vital for the organism's survival and are in constant communication in pursuit of maintaining or restoring homeostasis [21, 112]. The brain integrates the immune system in the systemic effort to effectively cope with stressors such as invasive agents or tissue injuries [100].

The brain's regulative control provides distinct advantages for the immune system. Specifically, the nervous system's ability to transmit information at rapid speeds and to sense pathogens or tissue damage-associated factors ensures a fast and effective immune response [100]. Additionally, the brain is constantly monitoring the internal and external environment. It is able to synchronize the immune system with other systems and processes it is dependent on, like blood flow and the digestive system [100]. By combining information about the external environment gathered by the sensory organs, the brain can anticipate potential threats to the body's homeostasis and prepare the immune system accordingly [1, 15].

The homeostatic internal milieu is however not only challenged by viruses or bacteria, but also by physical exercise. Depending on the duration and intensity, exercise constitutes a stimulus that demands physiological and psychological resources [87]. The immunological response to the stressor is predominantly characterized by a short-term redistribution of immune cells into the circulation, their infiltration of tissues and a rise in the circulating levels of cytokines [30, 31, 35, 74, 87].

Previous studies indicate that this integration of the immune system into an orchestrated, systemic stress response is achieved either through the control of blood flow, metabolic activity or muscle action [24, 90, 91, 100] or directly via the efferent arms of several neuro-immune pathways. The sympathetic, parasympathetic, somatosensory, neuroendocrine and neurotrophic pathways act as interfaces between the nervous system and the immune system [29, 36, 50, 57, 58, 104, 110, 119]. Measuring specific biomarkers in the peripheral blood that are associated with the activity of these pathways such as adrenaline, noradrenaline, acetylcholine, cortisol, serotonin or brain-derived neurotrophic factor (BDNF), to name a few, allows a conclusion to be drawn about their involvement in the body's stress response and nature of the neuroendocrine-immune regulation. Although being primarily used for communication within the neuroendocrine system, the expression of specific receptors for these biomarkers on leukocytes lays the foundation for the functional connectivity between the nervous system, endocrine system and the immune system. Specific effects upon receptor binding include the exercise-induced redistribution of T-lymphocytes within lymphoid and non-lymphoid organs, mediated by α- and β-adrenoceptor signaling [71]. The general mobilization pattern of lymphocytes during exercise is related to the differential expression of β-adrenergic receptors on lymphocytes (Natural killer cells > CD8+ T-cells > B-cells > CD4+ T-cells) [11, 70, 115]. Furthermore, the noradrenaline-mediated CD4+ T-cell differentiation [21] or the acetylcholine-mediated attenuation of inflammation through the inhibited secretion of TNF, IL-1β, IL-6 and IL-18 by macrophages [104] are among the reported effects.

In recent years, central neuronal factors, such as BDNF, nerve growth factor (NGF) or serotonin that were previously associated with neurological processes gained increasing attention in the context of immunoregulation, as well. BDNF for example has been described to be an anti-apoptotic survival factor for B- and T-cells and to promote glial cell proliferation [53, 102, 125].

The response of the biomarkers of neuroendocrine-immune regulation to acute exercise stress is multifaceted and dependent on several exercise program variables like volume, intensity, duration and mode [18, 67]. For resistance exercise for instance, it has been demonstrated that, in general, protocols with a high intensity, high volume and short rest intervals cause the greatest elevations of circulating biomarkers [30]. Especially, increments of classical stress hormones such as adrenaline, noradrenaline and cortisol as well as of anabolic hormones such as growth hormone and neurotrophins have been documented in response to acute bouts of resistance exercise [28, 30, 67]. Literature comparing this reaction directly to endurance exercise is sparse. Evidence exists suggesting that the direction of the effects is similar, the magnitude might however differ owing to the fact that resistance and endurance exercise differ in terms of muscle fiber recruitment and hemodynamics [44], Additionally, the metabolic pathways used for energy production during exercise could give an indication for the biomarker response. Existing evidence indicates that at similar exercise intensities, higher rates of anaerobic glycolysis (e.g., during resistance exercise) lead to greater cortisol increments due to its relationship with lactate concentrations [3, 113].

As resistance exercise with heavy loads has been described to be more demanding with regards to the neuromuscular activity than with light loads [122], approaching changes in neuroendocrine-immune pathway activity from a standpoint of heavy resistance exercise appears to be worthwhile. However, to the author's knowledge, no systematic review to date has characterized the alterations in the activity of these pathways of neuroendocrine-immune regulation in response to an acute bout of heavy resistance exercise in healthy adults.

Therefore, the aim of this systematic review is to examine the acute effects of heavy resistance exercise on selected biomarkers of neuroendocrine-immune regulation in healthy adults.

METHODS

The protocol for this systematic review was prospectively registered with the Open Science Framework (https://osf.io/ebr4k). Amendments to the protocol can be accessed via the corresponding project (https://osf.io/a8b23/). It was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement [72].

Eligibility criteria

The eligibility criteria were formed a priori using the PICOS (participants, intervention, comparators, outcomes, and study design) approach.

Inclusion criteria were defined as follows: (1) participants: a cohort of healthy adults (18 years of age or older) (2) intervention: single session of heavy resistance exercise, defined as concentric and eccentric muscle actions to overcome externally applied resistance with a load of more than 80% of the individual's one repetition maximum (1RM) or

100% of the 1-8RM (3) outcomes: blood plasma or serum measurements of at least one of the following biomarkers of neuroendocrine-immune regulation at rest and follow-up (within 60 minutes after termination of exercise): Adrenaline, noradrenaline, acetylcholine, vasoactive intestinal peptide (VIP), cortisol, growth hormone, CGRP, substance p, serotonin, BDNF, nerve growth factor (NGF) and glia-derived neurotrophic factor (GDNF) (4) study design: clinical trials (5) studies published in a peer-reviewed journal in English or German.

Exclusion criteria were defined as follows: (1) a cohort with subjects below 18 years of age or with health problems (e.g., diabetes mellitus or multiple sclerosis) (2) resistance exercise that was combined with other treatment modalities that could alter the physiological response to exercise (e.g., blood flow restriction or pharmacological supplementation), that used a load that was lower than 80% of the 1RM and/or that was used as a follow-up measurement in a training intervention program (3) no baseline measurement or a follow-up measurement that was conducted later than 60 minutes after termination of the exercise (4) reviews, cross-sectional or retrospective longitudinal study designs, meeting abstracts and conference proceedings, letters to the editor or records with no identifiable abstract (5) studies published in other languages than English or German.

Literature search

The literature search was conducted in March 2021 in the electronic databases PubMed, Web of Science, Cochrane CENTRAL Library and SportDiscus with no restrictions on date, publication type or language. The search terms were collected through experts' opinion, literature scoping and related vocabulary. They covered the following domains: resistance training, biomarkers and blood sample (serum and plasma). The exact search syntax for each database can be accessed via the aforementioned link to the Open Science Framework. In order to identify further studies the reference lists of included studies were examined and key journals hand searched.

Study selection

The identified records were downloaded from the electronic databases and managed in Zotero (version 5.0.96.2). After the detection and deletion of duplicates, the records were exported to Rayyan (https://rayyan.qcri.org), a free web-based platform that enables a collaborative record management. In Rayyan relevant studies were independently selected in a two-stage process by SH and MR. In the first stage, titles and abstract were screened. The studies that did not meet the eligibility criteria were excluded. In the second stage, the full-text articles of the remaining studies were accessed. Studies that were considered eligible after screening of the full text were included into the review process. Cases of disagreements were solved by discussion at the end of both stages. If necessary, a third reviewer was consulted for clarification.

Reasons of exclusion in the second stage were documented and can be observed in Figure 1 together with all other information on the selection process.

Data extraction

The data extraction was performed by SH and verified by a second reviewer. Cases of disagreements were solved by discussion. The following data items were extracted from the included studies using a standardized form in Microsoft Excel: the authors, year of publication, pre-post intervention group sample size and participant characteristics including sex, age, height, weight and resistance training experience. Participants were deemed inexperienced if their absence of experience was explicitly stated or if they were not involved in any form of resistance exercise within the last three months prior to testing. Furthermore, the exercises performed, training volume and intensity, time of day, biomarkers measured, follow-up measurement intervals, blood samples used, analysis methods, as well as the main outcome related findings and baseline and follow-up concentrations of the biomarkers were extracted. If biomarker concentrations were not provided in the studies, the first and last authors were contacted via their institutional mail addresses. The WebPlotDigitizer digitization program (https://automeris.io/WebPlotDigitizer/) was used to extract plotted data if authors did not respond within one month.

Study quality

The risk of bias of the included studies was independently assessed by SH and CP using a modified version of the quality appraisal tool developed by Brook Galna and colleagues [34]. The tool consists of 14 questions focusing on the external validity, internal validity and reproducibility of the study. Each question was scored on a scale of zero to one, where one indicates high quality and zero low quality. For the purpose of this review, the fifth item of the original tool was left out, taking the different methodological approaches of the studies included in the present review and the review by Galna et al. into account.

Data synthesis

The results of the literature search, the study and sample characteristics and risk of bias assessment were summarized in figures and tables. Given the fact that the included studies did not provide standard deviations, variances, precise p-values or effect estimates, the effect of heavy resistance exercise on the biomarker levels was computed as the percentage change from a resting baseline value to the immediate post-exercise value. In accordance with the Cochrane Handbook for Systematic Reviews of Interventions [81], the narrative summary of the effects was complemented by the effect distributions (median, range, interquartile range) for each biomarker computed in R Studio (Version 1.4.1106). Furthermore, the magnitude and direction of the effects on the study levels were displayed using bar charts.

RESULTS

Study selection

A total of 7801 records were identified through database searching (PubMed: 1404, Web of Science: 4458, Cochrane: 971, SportDiscus: 968). After the removal of duplicates, 5726 studies were screened by titles and abstracts. Of these, 5678 records were removed, leaving 48 eligible for full-text screening. A further 14 articles were removed, and 2 records

were added through hand-searching key journals and reference lists, resulting in 36 articles with a total of 58 pre-post intervention groups that met the inclusion criteria and were included into the qualitative synthesis. The studies by Church et al. [13] and Mangine et al. [75] as well as by Rahimi et al. [96] and Rahimi et al. [97] were published based on the same experiments, respectively. Since they are separate publications reporting the effects on different outcome measures, they were not treated as duplicate studies. The search and study selection process are detailed in Figure 1.

All the resistance exercise interventions conducted in the 36 studies included a lower body exercise, of which 30 (83%) included multi-joint lower body exercises. 20 studies (56%) added upper body exercises to the protocol. The exercise sessions were predominately (56%) conducted in the morning hours. The session volume, expressed as the total number of repetitions, ranged between 8 and 280. All studies, except for five that used the high-performance liquid chromatography (HPLC), used immunoassays to analyze blood samples, with the enzyme-linked immunosorbent assay (ELISA) and

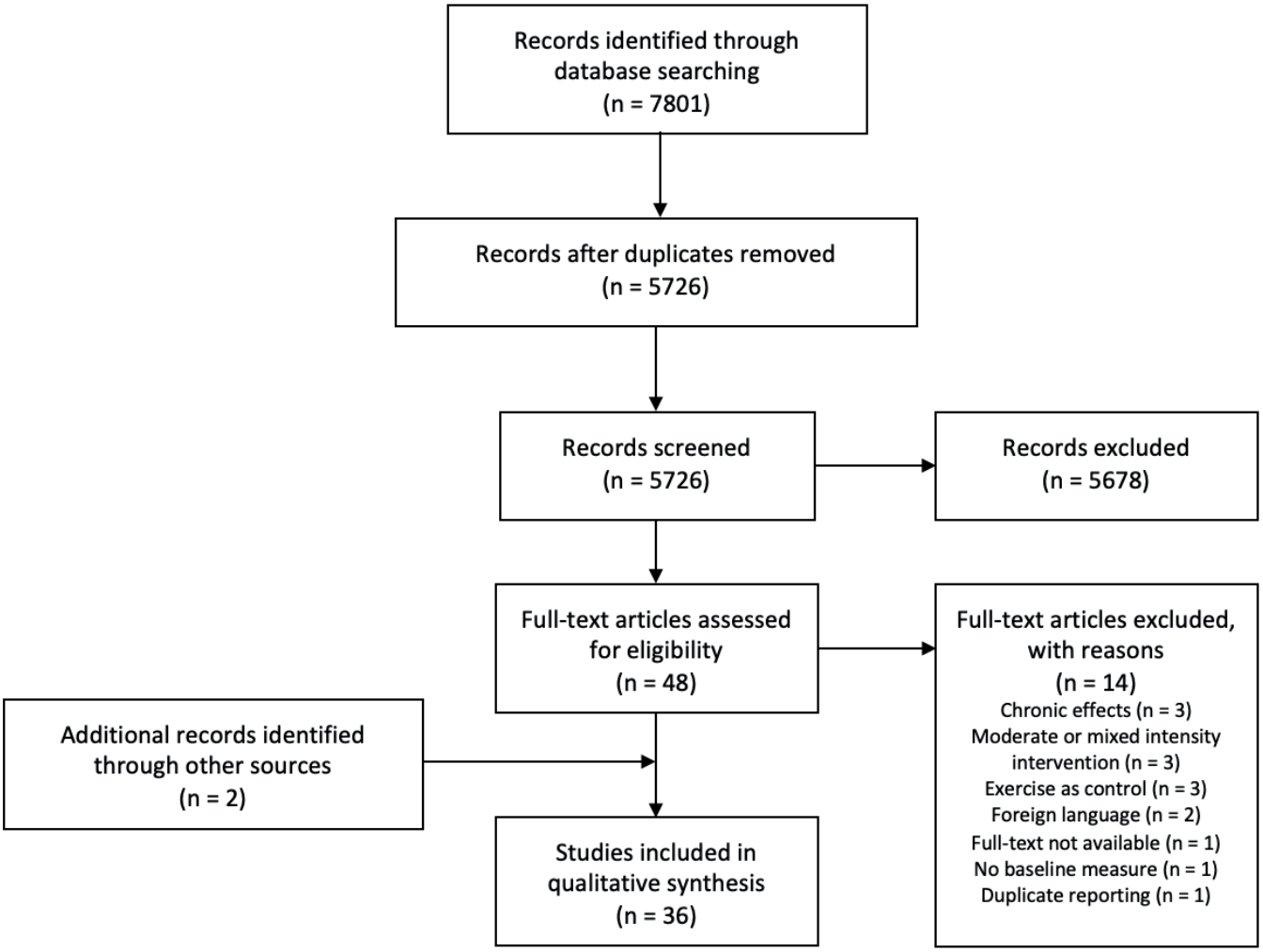

Figure 1. Flow diagram of literature search and study selection

Study characteristics

A detailed summary of the characteristics of the included studies is presented in Table 1. All articles were published in English between the years 1990 and 2020. Seven studies (19%) included a sample of men and women, while 25 studies (69%) recruited only men and three studies (8%) only women. One study (3%) did not report the sex proportion. The mean age of the subjects in the included intervention groups was 27.5 years, with a range from 18 to over 72 years. The participants of eight studies (22%) were deemed inexperienced with regards to resistance training, while 21 studies (58%) included participants with some form of resistance training experience, either as recreational (n=19) or professional athletes (n=3). One study (3%) included both inexperienced subjects and professional athletes and five studies (14%) did not report the resistance training experience of their participants.

radioimmunoassay (RIA) as the predominant choices. The reported intra-assay and inter-assay coefficients of variation were below 10%.

Quality assessment

The studies included into this systematic review stated their research aims clearly, with studies lacking detail or clarity in only two cases [52, 82]. The participants included in the studies were detailed sufficiently, the sampling and recruitment methods were however described unsatisfactorily, compromising the ability to repeat the studies appropriately. The repeatability of the study procedure was impaired in several cases due to the fact that it was not detailed at which time of the day the participants were tested and if they were sober or postprandial. Overall, the described methodology was able to answer the research question adequately. The

Reference	Design	N (m/f)	Age (years) M±SD	Resistance training level	Exercises	Volume Sets x Reps; Rest (mins)	Intensity	Time of day	Hormone	Sample	Analysis method	Follow-up measurement (mins)	Main outcome related findings
Bosco et al. (6)	Pre-post	12 (6/6)	m: 23.3±2.4 f: 23.0±2.7	NR	Half squat, full squat	6 x 16; 8	80% 1RM	10:00-12:30	C	Serum	RIA	0	1% decrease of C 0 mins post in women; 35%* decrease of C in men
Burley et al. (9)	Pre-post with control	24 (24/0)	21.4±1.9	Inexperienced	Leg press, chest press, lat. pull-down, shoulder press	3 x 10; 2	80% 1RM	08:00 or 18:00	C	Serum	ELISA	5	No change of C 5 mins post in morning, 6% increase in evening group; sig. higher C levels in morning session compared to evening
Church et al. (13)	Pre-post	10 (10/0)	22.6±2.3	Experienced	Back squats, deadlifts, leg press, lat. pull-down, barbell rows, barbell curls	4 x 3-5; 3	90% 1RM	NR	BDNF	Plasma	ELISA	0, 30, 60	62%* increase of BDNF 0 mins post; stayed sig. elevated at 30 and 60
Cui et al. (19)	Pre-post	15 (NR)	18.9±0.1	Inexperienced	Bench press, squat, lat. pull-down, overhead press, standing dumbbell curl	4 x 6; 3	90% 1RM	16:00	C	Plasma	CLIA	0, 60	38%* increase of C 0 mins post; no sig. change between 0 and 60 mins post
Dalbo et al. (20)	Pre-post	22 (22/0)	21±1 68±1	NR	Squats, leg press, leg extensions	3 x 10; 3	80% 1RM	06:00-09:00	C	Serum	ELISA	5	114%* increase of C in young and 167%* in old men 5 mins post
Doma et al. (23)	Pre-post	14 (14/0)	24.0±3.9	Inexperienced	Squats, single-leg leg press, leg extension, leg curls	3 x 6; NR	95% 6RM	NR	C	Serum	FIA	0	Sig. increase of C 0 mins post during first session; no sig. change during second visit 2 weeks later
Flynn et al. (27)	Pre-post with control	15 (0/15)	72.6±3.5	Inexperienced	Leg extension, leg curl, plantar flexion, dorsiflexion, leg abduction, leg adduction, hip extension, hip flexion	2-3 x 8; 2	80% 1RM	08:00	C	Serum	RIA	0	33%* decrease of C 0 mins post
Fragala et al. (31)	Pre-post with control	15 (8/7)	m: 24.6±5.1 f: 22.1±3.1	Experienced	Back squats	6 x 5; 3	90% 1RM	05:30-08:00	A, NA	Plasma	HPLC	0, 60	233%* and 424%* increase of A and NA in men, 131%* and 409%* increase of A and NA in women 0 mins post with no sig. gender difference; returned to baseline 60 mins post
French et al. (33)	Pre-post with control	10 (10/0)	23±2	Experienced	Smith's squats	6 x 10; 2	80% 1RM	07:00-10:00	A, NA	Plasma	RIA	0, 5	185%* and 149%* increase of A and NA 0 mins post; sig. anticipatory increase of A and NA immediately before compared to 60 mins before exercise
Goto et al. (40)	Pre-post	8 (8/0)	20-23	Experienced	Bilateral knee extension	5 x 5; 3	90% 1RM	NR	GH	Serum	RIA	5, 15, 30, 60	Small increase of GH post exercise which is not reported to be significant
Goto et al. (41)	Pre-post	6 (6/0)	24.3±0.4	Experienced	Bilateral knee extension	5 x NR; 1	80% 1RM	08:00-12:00	A, NA C, GH	Plasma Serum	HPLC RIA	5, 15, 30	73%* and 113%* increase of A and NA 5 mins post; returned to baseline 15 mins post 18% and 882% increase of C and GH 5 mins post; decrease of C, further increase of GH during recovery
Goto et al. (39)	Pre-post	9 (9/0)	24±0.2	Experienced	Bilateral knee extension	4 x 9; 1	80% 1RM	08:00-12:00	A, NA C, GH	Plasma Serum	HPLC RIA	0, 15, 30	262%* and 314%* increase of A and NA 5 mins post; returned to baseline 15 mins post 16% and 12% increase of C and GH 5 mins post; decrease of C, further increase of GH during recovery
Häkkinen and Pakarinen (45)	Pre-post with control	10 (10/0)	29.7±8	Professional athletes	Back squat	20 x 1; 3	100% 1RM	17:00-19:00	C, GH	Serum	RIA	0, 60	7% decrease of C 0 mins post; sig. decrease from 0 to 60 mins post 361%* increase of GH 0 mins post; sig. decrease from 0 to 60 mins post
Jablu and Hosseini (49)	Pre-post with control	10 (0/10)	54.3±3.7	NR	Supine chest press, lat. pull-down, leg press, biceps curl, triceps pushdown, leg curl, leg extension. shoulder press	3 x 10; 1	80% 1RM	08:00-10:30	C	Serum	CLIA	0, 15	35% decrease of C 0 mins post
Jin et al. (52)	Pre-post	10 (10/0)	20.8±1.4	NR	Exercise circuits: bench press, seated cable row, sit-up, leg extension, leg curl	5-10 x 8; 0.5	85% 1RM	NR	C	Serum	RIA	0, 30	26%* increase of C 0 mins post; stayed sig. increased 30 mins post
Kokalas et al. (60)	Pre-post with control	6 (6/0)	20±1.6	Professional athletes	Bench pulls in prone position, leg press in sitting position, rowing from standing position	6 x 6; 2	85-100% 1RM	08:00-09:00	C, GH	Serum	ELISA	0	36% decrease of C and 2633% increase of GH 0 mins post, significance level NR

Reference	Design	N (m/f)	Age (years) M±SD	Resistance training status	Exercises	Volume Sets x Reps; Rest (mins)	Intensity	Time of day	Hormone	Sample	Analysis method	Follow-up measurement (mins)	Main outcome related findings
Kraemer et al. (65)	Pre-post	9 (9/0)	24.7±4.3	Experienced	Bench press, bilateral leg extensions, military press, sit-ups, seated rows, lat. pull-downs, arm curls, leg press	3-5 x 5; 3 or 1	100% 5RM	NR	GH	Serum	RIA	0, 5, 15, 30, 60	252%* and 330%* increase of GH in 3 and 1 mins rest protocol 0 mins post; returned to baseline 5 and 15 mins post in 3 and 1 mins rest protocol respectively Increase sig. greater with shorter rest
Kraemer et al. (66)	Pre-post	16 (8/8)	m: 24.7±4.5 f: 23.1±3.3	Experienced	Bench press, bilateral leg extensions, military press, sit-ups, seated rows, lat. pull-downs, arm curls, leg press	3-5 x 5; 3	80-95% 1RM	08:00-10:00	GH	Serum	RIA	0, 5, 15, 30, 60	75% increase of GH 0 mins post in men; further increase until 30 mins post; returned to baseline 60 mins post 26% decrease of GH 0 mins post in women; further decrease during recovery
Kraemer et al. (62)	Pre-post	9 (0/9)	24.1±4.3	Experienced	Bench press, bilateral leg extensions, military press, sit-ups, seated rows, lat. pull-downs, arm curls, leg press	3-5 x 5; 3 or 1	100% 5RM	08:00-10:00	C, GH	Serum	RIA	0, 5, 15, 30, 60	35% increase and no change of C in 3 and 1 mins rest protocol 0 mins post; no sig. change in both protocols during recovery 27% decrease and 24% increase of GH in 3 and 1 mins rest protocol 0 mins post; decrease below baseline in both protocols during recovery
Kraemer et al. (61)	Pre-post	8 (8/0)	24.7±1.6	Experienced	Bench press, bilateral leg extensions, military press, sit-ups, seated rows, lat. pull-downs, arm curls, leg press	3-5 x 5; 3 or 1	100% 5RM	NR	C	Serum	RIA	0, 5, 15	1% and 9% increase of C in 3 and 1 mins rest protocol 0 mins post; decrease below baseline in both protocols during recovery
Kraemer et al. (69)	Pre-post	21 (13/8)	m: 25.3±3.2 f: 20.6±1.5	Inexperienced	Squat, leg press, knee extension	3 x 6-8; 2	100% 6-8RM	NR	C, GH	Serum	RIA	0, 5	50%* and 1159%* increase of C and GH 0 mins post in men 7% and 265%* increase of C and GH 0 mins post in women
Kraemer et al. (63)	Pre-post	19 (19/0)	Athletes: 24.7±3.8 Untrained: 26.6±5.9	Professional athletes or Inexperienced	Bilateral leg press	1 x 20-21	80% 1RM	NR	A, C, NA	Plasma	HPLC, RIA	0,5	70%* and 95%* increase of A and NA and 21% decrease of C 0 mins post in athletes 68%* and 58%* increase of A and NA and 5% decrease of C 0 mins post in untrained subjects
Mangine et al. (75)	Pre-post	15 (15/0)	24.7±3.4	Experienced	Back squats, deadlifts, leg press, lat. pull-down, barbell rows, barbell curls	4 x 3-5; 3	90% 1RM	NR	C, GH	Serum	ELISA	0, 30, 60	22%* decrease of C and 119% increase of GH 0 mins post; C stayed below and GH decreased below baseline during recovery
Marston et al. (77)	Pre-post	16 (11/5)	m: 25±1.3 f: 23.2±1.3	Inexperienced	Bench press, lat. pull-down, leg press, leg extension, seated row, military press, dumbbell arm curl	5 x 5; 2	100% 5RM	NR	BDNF	Serum	ELISA	0, 30	1% decrease of BDNF 0 mins post, decrease below baseline during recovery
Marston et al. (76)	Pre-post	14 (NR)	55.2±6.8	Inexperienced	Bench press, leg press, lat. pull-down, leg curl	5 x 5; 2	85% 1RM	NR	BDNF	Serum	ELISA	0, 30	3% increase of BDNF 0 mins post, decrease below baseline during recovery
McMurray et al. (82)	Pre-post with control	8 (8/0)	18-30	Experienced	Circuit: Leg press, bench press, leg extension, lat. pull-down, leg curl, military press	3 x 6-8; NR	80% 1RM	18:00	C, GH	Plasma	RIA	0, 20, 40, 60	17% increase of C 0 mins post; peak at 20 and decrease below baseline at 60 mins 2835%* increase of GH 0 mins post; stayed sig. elevated and returned to baseline 60 mins post
Pareja-Blanco et al. (89)	Pre-post	10 (10/0)	22.1±3.5	Experienced	Smith's bench press, Smith's squat	3 x 8, 6 or 4; 5	80, 85 or 90% 1RM	10:00	C, GH	Plasma	ECLIA	5	Sig. decrease of C 5 mins post in 4 reps without failure protocol; no sig. change in all other protocols No sig. change of GH 5 mins post regardless of protocol
Pullinen et al. (94)	Pre-post	17 (9/8)	m: 29±3 f: 27±4	Experienced	Bilateral knee extension	1 x 8-10	80% 1RM	NR	A, NA	Plasma	HPLC	0	315% and 74%* increase of A and NA 0 mins post in men 264% and 38% increase of A and NA 0 mins post in women
Raastad et al. (95)	Pre-post with control	9 (9/0)	26.9±1.4	Professional athletes	Back squats, front squats, leg extensions	3 x 3-6; 4-6	100% 3-6RM	08:30-10:00	ACTH C, GH	Plasma Serum	ILMA RIA, IRMA	0, 15, 30, 45, 60	43% and 24% decrease of ACTH and C 0 mins post, no significance reported 1462% increase of GH 0 mins post Gradual decrease during recovery
Rahimi et al. (97)	Pre-post with control	10 (10/0)	22±2	Experienced	Squat, bench press	4 x NR; 1, 1,5 or 2	85% 1RM	09:00-11:00	GH	Serum	ELISA	0, 30	208%*, 142%* and 133% increase of GH 0 mins post in 60, 90 and 120 secs rest protocols

Reference	Design	N (m/f)	Age (years) M±SD	Resistance training status	Exercises	Volume Sets x Reps; Rest (mins)	Intensity	Time of day	Hormone	Sample	Analysis methods	Follow-up measurement (mins)	Main outcome related findings
Rahimi et al. (96)	Pre-post with control	10 (10/0)	22±2	Experienced	Squat, bench press	4 x NR; 1, 1,5 or 2	85% 1RM	09:00-11:00	C	Serum	ELISA	0, 30	93%*, 63%* and 13% increase of C 0 mins post in 60, 90 and 120 secs rest protocols
Smilios et al. (108)	Pre-post with control	11 (11/0)	23±4	Experienced	Bench press, lat. pulldowns, squat, overhead press	2, 4 or 6 x 5; 3	80-88% 1RM	09:00 or 11:30	C, GH	Serum	LIA, IRMA	0, 15, 30	18%*, 18%* and 24%* decrease of C 0 mins post in 2,4 and 6 set group; stayed below baseline during recovery 141%*, 448%* and 383%* increase of GH 0 mins post in 2,4 and 6 set group; stayed below baseline during recovery; returned towards baseline 30 mins post
Tsai et al. (114)	Pre-post with control	20 (20/0)	22.4±2.4	NR	Bench press, biceps curls, triceps extensions, leg press, vertical butterflies, leg extensions	2 x 10; 1.5-2	80% 1RM	Morning	C, GH	Serum	ELISA, CLIA	5	13%* decrease of C 5 mins post; 1157%* increase of GH 5 mins post
Walker et al. (123)	Pre-post with control	13 (13/0)	28.4±3.7	Inexperienced	Leg press	15 x 1; 3 or 5 x 10; 2	100% 1RM or 80% 1RM	M: 15:45	C, GH	Serum	CLIA	0, 15, 30	Exercise with variable loads induced sig. increase of C and GH 0, 15 and 30 mins post in 80% intensity group; C didn't change sig. and GH increased sig. 0 mins post in 100% group; Exercise with constant load induced no sig. change of C or GH in 100% group; C and GH increased sig. 15 and 30 mins post in 80% group
Wells et al. (126)	Pre-post	10 (10/0)	24.7±3.4	Experienced	Back squats, bilateral leg press, bilateral hamstring curls, bilateral leg extensions, seated calf raises	4-6 x 3-5; 3	90% 1RM	Morning	C	Plasma	ELISA	0, 30, 60	21% increase of C 0 mins post; decrease below baseline during recovery
Zafeiridis et al. (128)	Pre-post with control	10 (10/0)	22.8±4.1	Experienced	Bench press, lat. pulldowns, squat, overhead press	4 x 5; 3	88% 1RM	09:00-11:30	C, GH	Serum	LIA, IRMA	0, 30	18% decrease of C 0 mins post, stayed below baseline during recovery 400%* increase of GH 0 mins post; returned towards baseline 30 mins post

A adrenaline; *BDNF* brain-derived neurotrophic factor; *C* cortisol; *CLIA* Chemiluminescence immunoassay; *ECLIA* Electrochemiluminescence immunoassay; *ELISA* Enzyme-linked immunosorbent assay; *f* female; *FIA* Fluorescence immunoassay; *GH* growth hormone; *HPLC* High-performance liquid chromatography; *ILMA* Immunoluminometric assay; *IRMA* Immunoradiometric assay; *LIA* Luminescence immunoassay; *m* male; *M* mean; *mins* minutes; *N* number of participants in the included intervention groups; *NA* noradrenaline; *NR* not reported; *Reps* repetitions; *RIA* radioimmunoassay; *RM* repetition maximum; * significantly different from baseline value at $p < 0.05$

Table 1. Subject and intervention characteristics and results of the included studies

key outcome variables were described clearly in all studies. The majority of the studies described the reliability of the key outcome measures, while no study detailed their internal validity. The results of the studies were discussed adequately, although only eight studies stated the clinical implications clearly. The exact quality assessment scores of all included article are presented in Table 2.

Acute effects on primary outcomes

There were no studies identified through the database search that investigated the acute effects of heavy resistance exercise on acetylcholine, VIP, CGRP, substance p, serotonin, NGF or GDNF. Consequently, results are presented for cortisol, ACTH, GH, adrenaline, noradrenaline and BDNF, assigned to the respective pathway of neuroendocrine-immune regulation they are associated with.

Sympathetic pathway

Changes in the circulating levels of adrenaline and noradrenaline in response to a heavy resistance exercise bout were measured by 6 studies, including a total of 9 intervention groups [31, 33, 39, 41, 63, 94].

Immediate effects

All included studies reported an immediate increase in the peripheral concentrations of adrenaline and noradrenaline after the termination of the resistance exercise session. All studies recruited resistance training experienced participants and only one study [63] included an additional intervention group of untrained participants. Still, differences in the magnitude of the changes became apparent, although there were no studies involved comparing variables like session volume, rest period or muscle mass involved.

The increase of adrenaline across the studies and intervention groups ranged from 68% to 315%, with a median (IQR) increase of 185% (73-262) (see Figure 2A). The most prominent increase was elicited by the resistance exercise bout employed by Pullinen et al. [94], despite the fact that it exhibited the lowest volume across the studies (8-10 total repetitions per session) using a single-joint knee extension exercise. On the contrary, another study using a protocol with an identical intensity in terms of the relative load used, repetitions in reserve and a similar volume reported the smallest increase among the studies investigating catecholamines [63]. The comparison of the immediate response of adrenaline showed that, although the absolute concentrations post-exercise were significantly greater for athletes compared to untrained individuals (no significance level reported), both groups changed to a similar degree, suggesting that there was no considerable influence of exercise experience on the acute adrenaline response [63].

The increase of noradrenaline across the studies and intervention groups ranged from 38 to 424%, with a median (IQR) increase of 113% (74-314) (see Figure 2B). The results of the studies indicated that protocols using only one set elicited the smallest increase across the studies, while those that used multiple sets of one exercise listed greater increases. In contrast to adrenaline, Kraemer et al. [63] showed that the increase of noradrenaline was significantly greater (no significance level reported) for athletes than for untrained subjects.

Studies comparing the catecholamine responses of men and women did not report any significant differences in the absolute levels of adrenaline or noradrenaline, neither before nor after the exercise bout between both sexes. Still, the relative changes from baseline to post-exercise suggest a trend towards slightly more pronounced catecholamine increases in men compared to women [31, 94]. Additionally, there is evidence from a study that took multiple blood samples before and during the exercise bouts that catecholamines increase in anticipation of the exercise stimulus and might already peak during the exercise protocol [33].

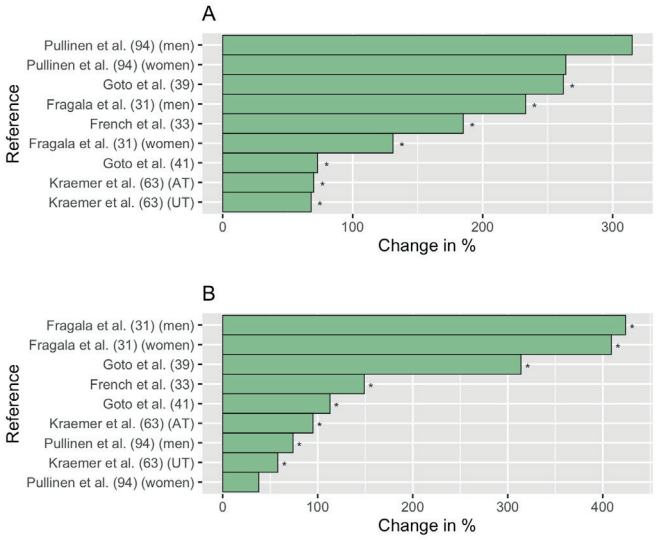

Figure 2. Immediate effects (0-5 minutes post-exercise) of heavy resistance exercise on **A** Adrenaline and **B** Noradrenaline expressed as change in %; * significantly different from baseline value at $p < 0.05$. AT=Professional athletes; UT=Untrained subjects

10-60 minutes post-exercise

Three of the six studies that investigated the catecholamine response to a resistance exercise session conducted follow-up measures during the recovery period [31, 39, 41]. None of the studies observed a significant difference in recovery values between the recovery period and their respective baselines. All of them reported that adrenaline and noradrenaline gradually decreased towards the baseline value at 15, 30 and 60 minutes into recovery.

Neuroendocrine pathway

A total of 26 studies with 46 intervention groups [6, 9, 19, 20, 23, 27, 39, 41, 45, 49, 52, 60–63, 69, 75, 82, 89, 95, 96, 108, 114, 123, 126, 128] and 18 studies with 34 intervention groups [39–41, 45, 60, 62, 64, 65, 69, 75, 82, 89, 95, 97, 108, 114, 123, 128] investigated the acute response of cortisol and GH respectively. One study also described the changes of ACTH in response to heavy resistance exercise [95].

Immediate effects

The results of the studies investigating the immediate effect of resistance exercise on the hormones of the neuroendocrine pathway revealed different response patterns for the different hormones in both the magnitude and the direction of the change. The peripheral concentration of ACTH was described to exhibit a decrease following a lower body resistance exercise bout in the morning [95]. The authors reported that the ACTH response appeared to be associated with the response of

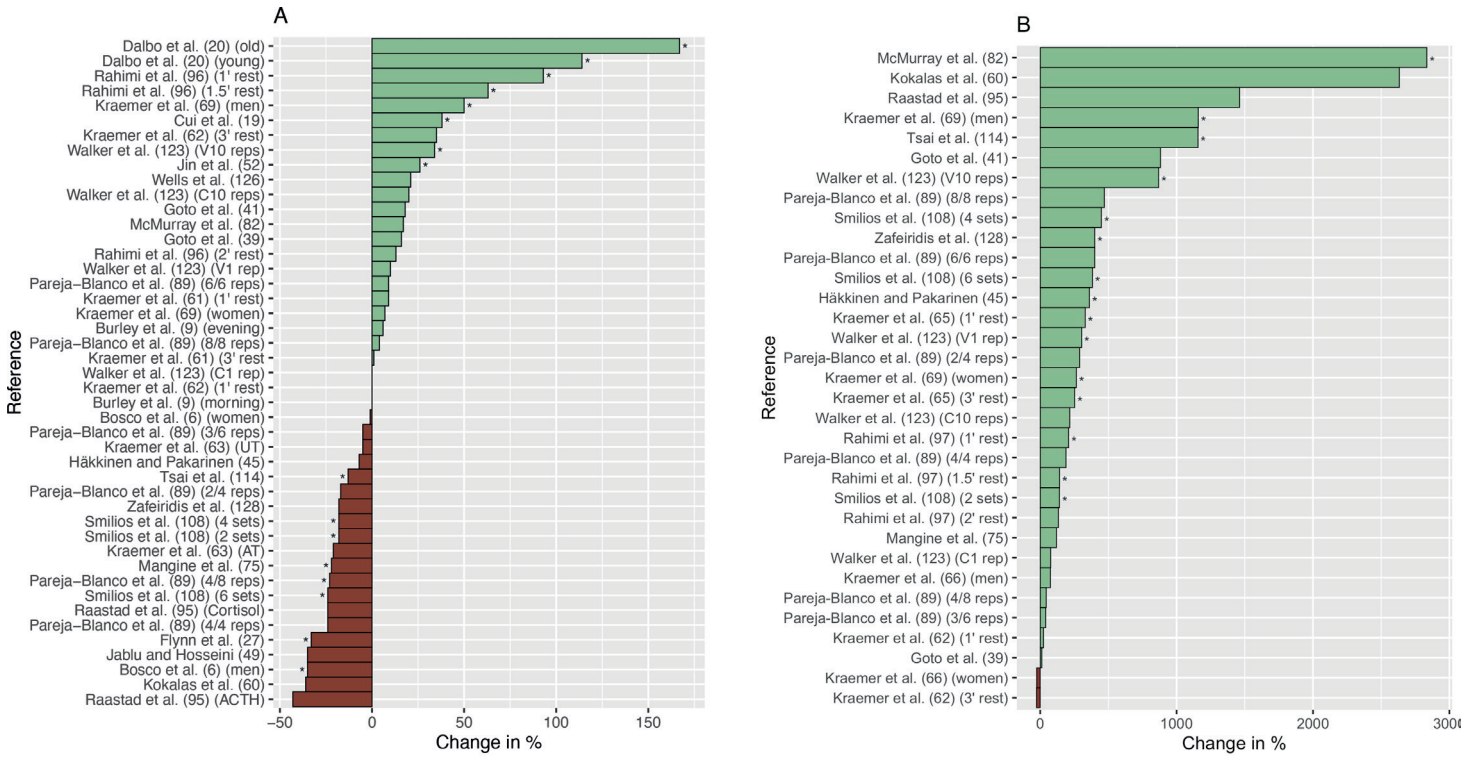

Figure 3. Immediate effects (0-5 minutes post-exercise) of heavy resistance exercise on **A** Cortisol and **B** Growth Hormone expressed as change in %; * significantly different from baseline value at $p < 0.05$. AT=Professional athletes; UT=Untrained subjects; C1/10 rep(s)=1/10 repetition(s) with constant resistance; V1/10 rep(s)=1/10 repetition(s) with variable resistance; 2/4 reps=half-maximal repetitions, 4 intended but 2 executed; 4/4=maximal repetitions, 4 executed

cortisol that decreased to a smaller amount [95].

Nonetheless, overall, the results regarding the direction of the change of cortisol following resistance exercise remained contradictory as they ranged from -48% to 167% across the included studied and intervention groups (see Figure 3A). The median (IQR) change of 0% (-18-18) shows that the participants in one half of the intervention groups exhibited an increase, while the other half exhibited a decrease in the circulating concentrations of cortisol immediately after the session. The exercise protocols of half of the intervention groups resulted in changes between -18% and 18%. The magnitude of the change appears to be associated with the sex of the investigated participants, with two studies reporting more pronounced responses in males compared to females [6, 69]. While males exhibited significant increases and decreases of cortisol immediately after exercise, the levels remained almost unchanged in females [6, 69]. A study by Dalbo and colleagues (2011) reported the biggest increase of cortisol following a lower body exercise bout performed by a group of young and a group of old men. They detected that the absolute peripheral cortisol concentrations were lower in older subjects at baseline and post-exercise. Nevertheless, the increase of cortisol was more pronounced in older subjects [20]. The influence of training status on cortisol alterations was only investigated in one study that reported no significant differences in the absolute levels between athletes and untrained subjects at baseline or follow-up but showed a slightly bigger decrease in athletes [63]. Studies investigating young male subjects with resistance training experience found that shorter inter-set rest intervals of one minute induced greater changes than two or three minutes of rest respectively [61, 96]. Yet, the opposite results were discovered with young resistance trained women when using the same exercise protocol, showing greater changes with longer rest periods [62]. Burley et al. [9] observed the circadian influence on the absolute peripheral cortisol concentrations as they showed significantly greater ($p < 0.001$) levels during a morning compared to an evening whole body exercise bout. The changes from baseline to post-exercise however did not seem to be influenced by the time of the day [9]. The comparison of 6 exercise protocols, of which three were performed with the maximum number of repetitions until fatigue was reached and three with half of the maximum number of repetitions revealed no clear evidence that the cortisol response is dependent on the number of repetitions in reserve or muscular fatigue [89]. It could however be shown that the two protocols with the highest session volume were the only two to induce cortisol increments post-exercise [89]. Similarly, an investigation comparing two exercise protocols involving variable resistance with two protocols involving constant resistance showed that in both protocols the bouts with the respective higher volume induced a greater cortisol increase [123]. Smilios et al. [108] on the other hand found no considerable differences between the changes induced by a 2-, 4- or 6-set protocol, as all of them decreased to similar amounts.

The change of growth hormone ranged from -27% to 2835% across studies and intervention groups, with a median (IQR) increase of 265% (119-448) (see Figure 3B). A comparison of the GH responses of men and women revealed that men tended to exhibit greater increments of GH immediately after a resistance exercise bout. The magnitude of these increases as well as the disparity between the responses of men and women were greater in a study including resistance trained

Criteria	Scoring	Bosco et al. (6)	Burley et al. (9)	Church et al. (13)	Cui et al. (19)	Dalbo et al. (20)	Doma et al. (23)	Flynn et al. (27)	Fragala et al. (31)	French et al. (33)	Goto et al. (40)	Goto et al. (41)	Goto et al. (39)	Häkkinen & Pakarinen (45)	Jablu & Hosseini (49)
1. Research aims or questions stated clearly	1 – Yes; 0.5 – yes, lacking detail or clarity; 0 – no	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2. Participants detailed	1–Yes; 0 – no														
Number		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Age		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Sex		1	1	1	0	1	1	1	1	1	1	1	1	1	1
Height		1	0	1	0	0	1	1	1	1	1	1	1	1	1
Sub Total		1	0.75	1	0.5	0.75	1	1	1	1	1	1	1	1	1
3. Recruitment and sampling methods described	1 – Yes; 0.5 – yes, lacking detail or clarity; 0 – no	0.5	0	0	0.5	0	0	1	0	0.5	0.5	0	0.5	0.5	0.5
4. Inclusion and exclusion criteria detailed	1 – Yes; 0.5 – yes, lacking detail or clarity; 0 – no	0.5	0.5	0.5	1	1	0.5	1	0.5	0.5	0.5	0	0.5	0.5	1
5. Key outcome variables clearly described	1 – Yes; 0.5 – only some defined; 0.5 – yes, lacking detail or clarity; 0 – no	1	1	1	1	1	1	1	1	1	1	1	1	1	1
6. Adequate methodology able to repeat study	1 – Yes; 0 – no														
Participant sampling		0	0	0	0	0	0	1	0	1	1	0	0	1	1
Equipment		1	1	1	1	1	1	0	1	1	1	1	1	1	1
Procedure		1	1	0	0	1	0	0	1	1	0	1	1	1	1
Data processing		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Statistical analysis		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Sub total		0.8	0.8	0.6	0.6	0.8	0.6	0.6	0.8	1	0.8	0.8	0.8	1	1
7. Methodology able to answer research question	1 – Yes; 0 – no														
Participant sampling		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Equipment		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Procedure		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Data processing		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Statistical analysis		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Sub total		1	1	1	1	1	1	1	1	1	1	1	1	1	1
8. Reliability of the methodology stated	1–Yes; 0–no	1	1	1	0	1	1	1	0	1	0	0	1	1	0
9. Internal validity of the methodology stated	1–Yes; 0–no	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10. Research questions answered adequately in the discussion	1–Yes; 0–no	1	1	1	1	1	1	1	1	1	1	1	1	1	1
11. Key findings supported by the results	1–Yes; 0–no	1	1	1	1	1	1	1	1	1	1	1	1	1	1
12. Key findings interpreted in a logical manner which is supported by reference	1–Yes; 0–no	1	1	1	1	1	1	1	1	1	1	1	1	1	1
13. Clinical implications stated	1 – Yes; 0.5 – yes, lacking detail or clarity; 0 – no	0.5	0.5	0	0.5	1	1	1	1	1	1	1	1	1	1

Criteria	Scoring	Jin et al. (52)	Kokalas et al. (60)	Kraemer et al. (65)	Kraemer et al. (66)	Kraemer et al. (62)	Kraemer et al. (61)	Kraemer et al. (69)	Kraemer et al. (63)	Mangine et al. (75)	Marston et al. (77)	Marston et al. (76)	McMurray et al. (82)	Pareja-Blanco et al. (89)	Pullinen et al. (94)
1. Research aims or questions stated clearly	1 – Yes; 0.5 – yes, lacking detail or clarity; 0 – no	0.5	1	1	1	1	1	1	1	1	1	1	0.5	1	1
2. Participants detailed	1–Yes; 0 – no														
Number		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Age		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Sex		1	1	1	1	1	1	1	1	1	1	0	1	1	1
Height		1	1	1	1	1	1	1	1	1	0	1	1	1	1
Sub Total		1	1	1	1	1	1	1	1	1	0.75	0.75	1	1	1
3. Recruitment and sampling methods described	1 – Yes; 0.5 – yes, lacking detail or clarity; 0 – no	0	1	0	0	0.5	0	0.5	0	0.5	0	0.5	0	0.5	0
4. Inclusion and exclusion criteria detailed	1 – Yes; 0.5 – yes, lacking detail or clarity; 0 – no	0.5	0.5	0.5	0.5	1	0.5	0	0.5	0.5	0.5	0.5	0.5	1	0
5. Key outcome variables clearly described	1 – Yes; 0.5 – only some defined; 0.5 – yes, lacking detail or clarity; 0 – no	1	1	1	1	1	1	1	1	1	1	1	1	1	1
6. Adequate methodology able to repeat study	1 – Yes; 0 – no														
Participant sampling		0	1	1	1	1	1	1	1	1	0	0	0	1	0
Equipment		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Procedure		0	1	0	1	1	0	0	0	0	0	0	1	0	0
Data processing		0	1	1	1	1	1	1	1	1	1	1	1	1	1
Statistical analysis		1	1	0	0	1	0	0	1	1	1	1	1	1	1
Sub total		0.4	1	0.6	0.8	1	0.6	0.6	0.8	0.8	0.6	0.6	0.8	0.8	0.6
7. Methodology able to answer research question	1 – Yes; 0 – no														
Participant sampling		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Equipment		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Procedure		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Data processing		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Statistical analysis		0	1	1	1	0	1	1	1	1	1	1	1	1	1
Sub total		0.8	1	1	1	0.8	1	1	1	1	1	1	1	1	1
8. Reliability of the methodology stated	1–Yes; 0–no	0	1	1	1	1	1	1	1	1	1	1	0	0	0
9. Internal validity of the methodology stated	1–Yes; 0–no	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10. Research questions answered adequately in the discussion	1–Yes; 0–no	1	1	1	1	1	1	1	1	1	1	1	1	1	1
11. Key findings supported by the results	1–Yes; 0–no	1	1	1	1	1	1	1	1	1	1	1	1	1	1
12. Key findings interpreted in a logical manner which is supported by reference	1–Yes; 0–no	1	1	1	1	1	1	1	1	1	1	1	1	1	1
13. Clinical implications stated	1 – Yes; 0.5 – yes, lacking detail or clarity; 0 – no	0.5	1	0.5	0	0	0.5	0.5	0	1	0.5	1	0	1	0

Criteria	Scoring	Raastad et al. (95)	Rahimi et al. (97)	Rahimi et al. (96)	Smilios et al. (108)	Tsai et al. (114)	Walker et al. (123)	Wells et al. (126)	Zafeiridis et al. (128)
1. Research aims or questions stated clearly	1 – Yes; 0.5 – yes, lacking detail or clarity; 0 – no	1	1	1	1	1	1	1	1
2. Participants detailed	1–Yes; 0 – no								
Number		1	1	1	1	1	1	1	1
Age		1	1	1	1	1	1	1	1
Sex		1	1	1	1	1	1	1	1
Height		0	0	1	1	0	1	1	1
Sub Total		0.75	0.75	1	1	0.75	1	1	1
3. Recruitment and sampling methods described	1 – Yes; 0.5 – yes, lacking detail or clarity; 0 – no	0.5	0	0	0	1	0	1	0
4. Inclusion and exclusion criteria detailed	1 – Yes; 0.5 – yes, lacking detail or clarity; 0 – no	0	0.5	0.5	0	1	0	1	0
5. Key outcome variables clearly described	1 – Yes; 0.5 – only some defined; 0.5 – yes, lacking detail or clarity; 0 – no	1	1	1	1	1	1	1	1
6. Adequate methodology able to repeat study	1 – Yes; 0 – no								
Participant sampling		0	1	1	0	1	0	1	0
Equipment		1	1	1	1	1	1	1	1
Procedure		1	0	0	1	1	0	1	1
Data processing		1	1	1	1	1	1	1	1
Statistical analysis		1	0	1	1	1	1	1	1
Sub total		0.8	0.6	0.8	0.8	1	0.6	1	0.8
7. Methodology able to answer research question	1 – Yes; 0 – no								
Participant sampling		1	1	1	1	1	1	1	1
Equipment		1	1	1	1	1	1	1	1
Procedure		1	1	1	1	1	1	1	1
Data processing		1	1	1	1	1	1	1	1
Statistical analysis		1	1	1	1	1	1	1	1
Sub total		1	1	1	1	1	1	1	1
8. Reliability of the methodology stated	1–Yes; 0–no	1	1	1	1	0	1	1	1
9. Internal validity of the methodology stated	1–Yes; 0–no	0	0	0	0	0	0	0	0
10. Research questions answered adequately in the discussion	1–Yes; 0–no	1	1	1	1	1	1	1	1
11. Key findings supported by the results	1–Yes; 0–no	1	1	1	1	1	1	1	1
12. Key findings interpreted in a logical manner which is supported by reference	1–Yes; 0–no	1	1	1	1	1	1	1	1
13. Clinical implications stated	1 – Yes; 0.5 – yes, lacking detail or clarity; 0 – no	0	1	0.5	0.5	0.5	0.5	0.5	0

Table 2. Methodological quality of the included studies

inexperienced participants compared to those who already had some experience with resistance training [64, 69]. Across the included studies, the intervention groups investigating female subjects reported a median change of GH concentrations of -1%, while the intervention groups investigating male subjects reported a median increase of 304%. The findings regarding the potential influence of exercise parameters on the GH response suggest that the rest intervals between the sets influences the magnitude of the acute response to exercise. Two studies [62, 65] employing the same exercise protocol reported that the shorter rest interval of one minute induced greater increases in peripheral GH concentration than a three-minute rest interval [65]. This is supported by another study that described significant increases of GH in a one-minute rest interval protocol but no significant change in a two-minute protocol [97]. Another training variable that appears to influence the magnitude of the GH response is the number of repetitions that are left in reserve during a set. A study including ten young resistance trained males described greater increase of GH for sets that were performed to failure compared to those that required only the half-maximal number of repetitions [89]. Additionally, those sets that were performed with a higher number of repetitions and thus with a higher session volume led to greater increases of GH [89, 108, 123].

10-60 minutes post-exercise

13 studies offered insight into the recovery of cortisol concentrations following the immediate response to heavy resistance exercise. The early recovery period of cortisol between 10 and 30 minutes after the termination of the exercise bout was characterized by an unstable trajectory, without a clear perceptible pattern. Four studies [62, 95, 96, 108] reported an intervention group that exhibited a further gradual increase or decrease of cortisol concentrations in the early recovery period. Five studies [39, 41, 49, 61, 126] reported that in at least one of the investigated intervention groups the trajectories of the cortisol response changed and either decreased below the baseline value or changed towards the baseline value. In four studies [52, 75, 82, 128] the cortisol levels remained approximately at the same levels as immediately after the termination of the exercise session. 60 minutes after the termination of the exercise however, these studies reported a decrease of cortisol below the baseline value [75, 82]. This trend was also observed by all other studies that took follow-up measures at 60 minutes into recovery [45, 95, 126], except for one [19].

Although sex, rest intervals and the number of repetitions appeared to influence the immediate GH response there was no clear evidence that indicated an influence of these parameters on the recovery of GH levels post-exercise. While five studies [39, 41, 64, 97, 123] reported that GH increased further in at least one of the investigated intervention groups during the early recovery period (10-30 minutes), the majority of the studies that employed multiple follow-up measures described a decline of the GH levels 10-30 minutes into recovery. A study investigating 13 male participants before, 15 minutes and 30 minutes after leg press exercise reported that the GH concentrations further increased in the higher volume groups with a peak at 15 minutes, while they gradually decreased in the lower volume groups [123]. All studies that employed follow-up measures 60 minutes post-exercise described that peripheral GH decreased towards - or in most cases even below - the resting value [40, 45, 62, 64, 65, 75, 82, 95].

Neurotrophic pathway

Neurotrophic biomarkers were measured by three of the included studies in the form of BDNF [13, 76, 77], while there were no studies identified that examined NGF or GDNF.

Immediate effects

The general magnitude and direction of the change of BDNF in the circulation elicited by resistance exercise varied across the three studies with one reporting a significant increase [13] and two describing small changes in a negative [77] and positive direction [76]. The most prominent immediate change was detected by Church et al. [13]. In a study investigating ten young male subjects with resistance training experience blood was sampled before and during recovery after the very first resistance exercise session of an 8-week training program. The training session involving multiple muscle groups induced a statistically significant increase in peripheral BDNF concentrations of 63% ($p < 0.05$). Two studies conducted by Marston et al. [77] and Marston et al. [76] on the other hand were not able to detect any considerable changes of peripheral BDNF concentrations immediately after resistance exercise. In both investigations, the authors recruited subjects of both sexes without resistance training experience. The study including late-middle-aged adults reported a BDNF increase of 3% immediately after termination of the exercise session [76] (see Figure 4). BDNF levels of young adults showed a small decrease of -1%, even though they trained with a higher volume in an otherwise comparable protocol [77].

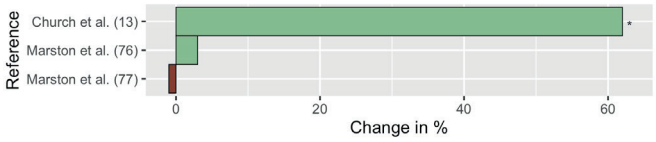

Figure 4. Immediate effects (0-5 minutes post-exercise) of heavy resistance exercise on Brain derived neurotrophic factor expressed as change in %; * significantly different from baseline value at $p < 0.05$.

10-60 minutes post-exercise

All three studies took follow-up measures during the acute recovery period. The trajectories of the biomarker concentrations during recovery mimicked the acute response in all studies, showing only small deviations from the immediate response. 30 minutes into recovery the circulating levels of BDNF decreased in both studies by Marston and colleagues slightly below the baseline and immediate post-exercise values. Similarly, Church et al. [13] reported a decrease of BDNF from 0 to 30 minutes post-exercise, even though it stayed statistically significantly elevated compared to baseline. 60 minutes into recovery however the levels increased again.

DISCUSSION

The aim of the present review was to examine the acute effects of heavy resistance exercise on selected biomarkers of neuroendocrine-immune regulation. These effects were defined as the change in the circulating concentration from a baseline resting level to a post-exercise level. To the authors'

knowledge this is the first systematic review to examine the acute response of these biomarkers to this specific type of exercise stimulus.

The findings of this systematic review revealed that the effects elicited by a heavy resistance exercise bout vary between the investigated biomarkers (see Figure 5).

finding of a general acute increase of catecholamine levels in response to heavy resistance exercise is in line with results of studies that characterized a release of catecholamines not only in response to physical stress like aerobic exercise [66] or moderate intensity resistance exercise [10, 43] but also as a result of cognitive stress [12].

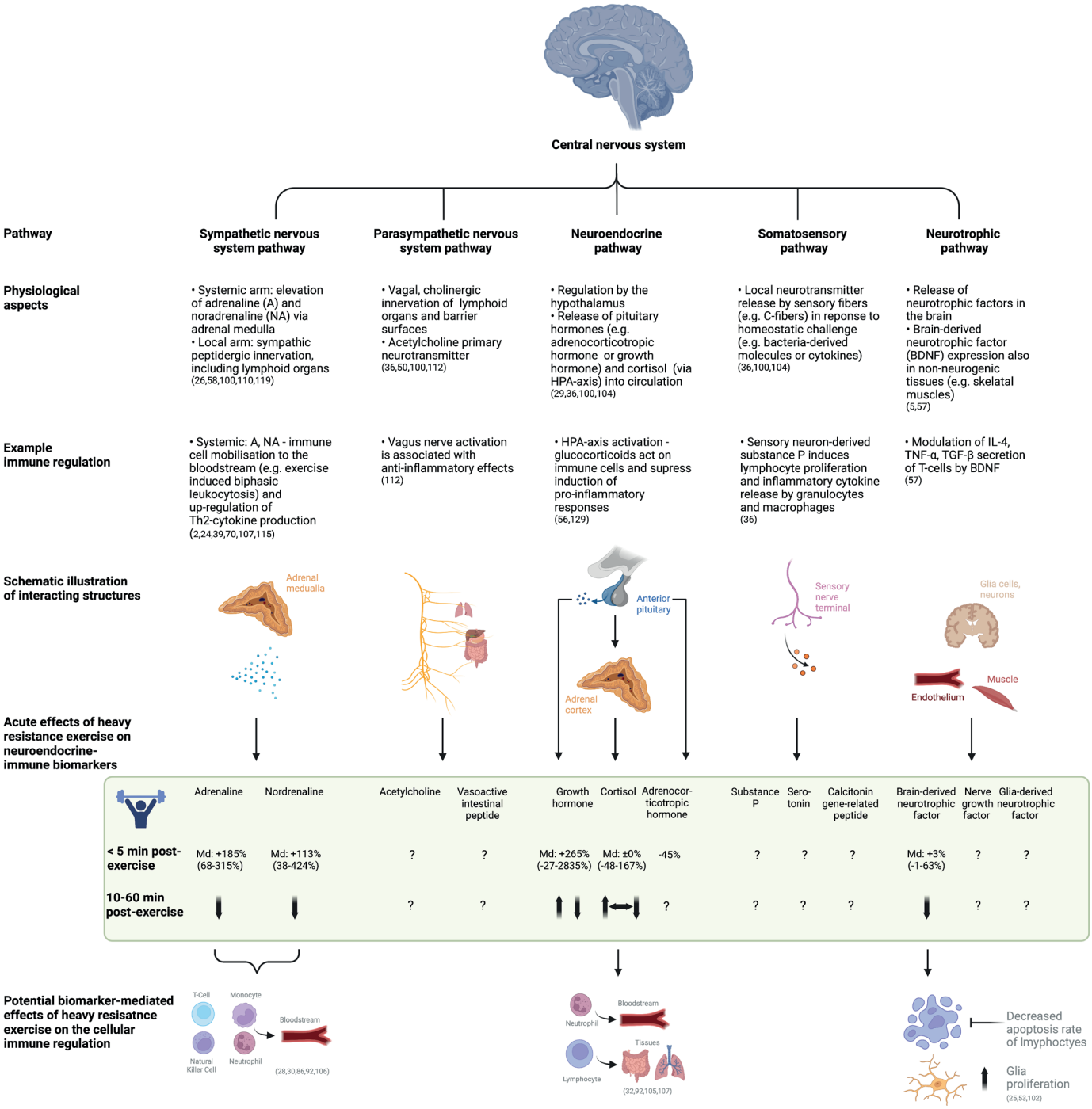

Figure 5. Investigated pathways of neuroendocrine-immune regulation, acute changes of associated biomarker concentrations following a bout of heavy resistance exercise and potential effects on the cellular immune regulation. The upwards arrow (🡅) indicates a further increase, the downwards arrow (🡇) a further decrease and the left-right arrow (🡘) no further changes of biomarker concentrations during recovery from a bout of heavy resistance exercise. HPA-axis=hypothalamic-pituitary-adrenal axis; Md=median (Graphic created with BioRender.com)

Even though the included studies employed different exercise protocols, adrenaline and noradrenaline were uniformly found to increase immediately after the termination of the exercise session and to gradually return to baseline during the first hour of recovery [31, 33, 39, 41, 63, 94]. The

This increased sympathetic signaling has previously been described as the organism's first response to a stressful stimulus to prepare and enable the body to cope with the stressful situation in the context of a fight-or-flight reaction [88]. Correspondingly, results provided in studies in the present

review suggest that peripheral catecholamine concentrations in¬ response to exercise already peak during the exercise period [33] and that the body releases catecholamines in anticipation of the stressor to be prepared once the resource demand increases [33, 63]. As the influence of individual training status and the sex of the participants has only been investigated by one [63] and two studies [31, 94], respectively, we cannot draw any firm conclusion on whether both parameters influence the acute sympathetic response. Still, the results of the studies give an indication that men, as well as athletes might experience greater increases of catecholamine levels in response to heavy resistance training compared to women and untrained individuals, respectively.

Systemically, the increased concentration of adrenaline and noradrenaline induces an increased heart rate, blood pressure and serum glucose levels as well as a bronchodilation [88]. However, it bears noting that noradrenaline is predominantly released by nerve terminals and should therefore be considered a neurotransmitter rather than a hormone [38]. Hence, plasma levels of noradrenaline are not always a reliable measure for sympathetic activity, as it exerts its effects rather locally than systemically [99]. Locally, it controls the vascular diameter and directs the peripheral blood distribution during daily activities, including exercise [38]. The higher increments of noradrenaline, but not of adrenaline, reported by Kraemer et al. [63] could therefore indicate that the sympathetic activity of athletes is characterized by a similar adrenal output, but greater noradrenaline release of sympathetic nerve terminals compared to untrained individuals. Irrespective of whether catecholamines are released via the adrenal medulla (80% adrenaline) or via postganglionic sympathetic nerve fibers in approximation with lymphoid target tissues like bone marrow, lymph nodes or mucosal barriers (mainly noradrenaline), their effects on the immune system are primarily mediated by β2-adrenergic receptors expressed by leukocytes [73, 88]. The stimulation of adrenergic receptors impacts immune cells with regard to their function, proliferation and trafficking [36, 119]. The most commonly reported effect of β-adrenergic signaling on the immune system is the mobilization and redistribution of leukocytes into the circulation [30, 92, 117]. An adrenaline-induced mobilization of NK-cells in response to running exercise in mice was for example described by Pedersen et al. [93]. On the contrary, the blockade of β-adrenergic receptors resulted in no leukocytosis after exercise [2]. The likelihood of any receptor interactions might be, at least for some leukocyte subpopulations, further facilitated by heavy resistance exercise. Fragala et al. [31] reported that the expression of β2-adrenergic receptors on lymphocytes was elevated after the termination of a heavy resistance exercise bout. The expression on monocytes was increased in anticipation of the exercise bout but decreased during the exercise period [31]. Furthermore, enhanced activation of postganglionic sympathetic nerve fibers in response to exercise could affect the lymphocyte function and proliferation in lymphoid organs like the thymus, spleen and lymph nodes. Accompanied by a transient noradrenaline release, a higher sympathetic activity has been reported to promote a Th2-cell cytokine profile [24, 36].

Similar to the acute catecholamine response, increments in GH concentration immediately after exercise were reported by all studies, except for two (see Figure 3B). It has also been a consistent finding among the studies that employed follow-up measures that the elevated levels of GH returned towards their resting values within the first hour of recovery, albeit only two studies detailed the design of the post-exercise period. The maximal increases however were bigger and the range of the effects among the studies broader, compared to adrenaline and noradrenaline. Acute increases of GH after resistance exercise have previously been described by many other studies employing moderate load resistance training [17, 42, 118]. Still, it should be mentioned that GH cannot be considered as a single substance but rather as a family of proteins with several isoforms and molecular weights [4, 68]. Studies investigating the trajectory of different GH isoforms in response to cycling [124] or resistance exercise [47] reported increases of almost all isoforms post-exercise. The relationships of the different isoforms did however change, as some increased more than others. It has been described that routine immunoassays will only analyze a specific spectrum of total GH isoforms, depending on their specificity [46, 103]. The isoform specificity can vary between immunoassay principle and between manufactures. A characterization is possible but rarely conducted in practice, a circumstance that may affect the comparability of the results [103]. The studies included in this systematic review did not differentiate between different isoforms and only two studies [75, 123] specified that they analyzed the isoform with a molecular mass of 22kDa. Thus, it cannot be determined with certainty which isoforms were respectively measured.

Evidence has been found that the aforementioned changes of GH levels post-exercise are in part influenced by participant characteristics and intervention parameters. Two studies included in the present review detected greater GH increments in men compared to women [64, 69]. According to earlier reviews, this sex difference is uniform across different exercise types and might be attributable to a greater growth hormone mass per burst and higher sensitivity of GH to GH-releasing hormone in women compared to men [18, 120]. Furthermore, it has been reported that the GH response to heavy resistance exercise tended to be more pronounced when the rest intervals between the sets were shorter [62, 65, 97] and the session volume higher [89, 108, 123]. These findings support the notion that volume and intensity are factors that determine the GH release. Elevations in the circulating levels of GH promote anabolic processes. It increases protein synthesis and reduces the breakdown of muscle protein [83]. Likewise, GH plays an important role for the development of lymphoid organs and the proliferation of T-cells. These effects are exerted directly via GH-receptor signaling, but also through up-regulation of other receptor types like androgen or angiotensin II-receptors [73]. Still, the acute contributions of GH to the immunoregulation in response to exercise are not well understood. It is assumed that GH does not play an important role in the mobilization of lymphocytes following exercise. Instead, it could act in concert with adrenaline and noradrenaline to recruit neutrophils into the circulation [92]. This evidence however comes from studies that administered GH intravenously or inhibited progenitors of GH during stressful events [92].

In contrast to the previously discussed biomarkers, the effects on cortisol were characterized by a variation in the direction of the change from baseline to immediately post-exercise. Out of all biomarkers investigated in this systematic review, cortisol was the most frequently measured. At the same

time, the results regarding the direction and magnitude of the immediate response to heavy resistance exercise are the most ambiguous. One half of the intervention groups investigated in the included studies exhibited an increase or no change of cortisol post-exercise, while the other half responded with no change or a decrease of cortisol (see Figure 3A). Previous reviews have reported that hypertrophy-based schemes with moderate loads uniformly induced increases of circulating cortisol levels that were on average greater than the alterations induced by strength-based schemes with heavy loads [18, 67]. Protocols that aim to increase muscle mass rather than strength usually use more repetitions, thus higher session volumes and shorter rest intervals. Consequently, they are considered to be more stressful and metabolically demanding, an assumption that is supported by the fact that hypertrophy-based protocols elicited higher lactate responses that are positively correlated with cortisol concentrations [67]. The release of the catabolic glucocorticoid into the circulation is meant to help the organism to cope with the stressful situation, for example by breaking down protein to provide glucose or by antagonizing the protein synthesis [88]. It is conceivable that some exercise protocols were not intense enough to force the body to mobilize resources through the activation of the hypothalamic-pituitary-adrenal axis. Correspondingly, based on the included studies, it can be assumed that the cortisol responses tend to be greater in protocols with shorter rest periods, higher volumes and with sets performed until volitional muscular fatigue was reached. Nevertheless, this trend can neither be confirmed nor ruled out with certainty, since among the concerning studies, two did not support this notion [62, 108].

In addition to this hypothesis, it is conceivable that the existence of cortisol-responder and non-responder participant characteristics contributed to the ambiguous results regarding the direction of the effect of exercise among the included studies. A study investigating 21 young male subjects for instance described two patterns of cortisol responses to a one-hour cycling bout [105]. 13 participants exhibited increased cortisol levels post-exercise, while eight subjects did not show any increments in cortisol levels, even though there were no differences in terms of age, physical build, aerobic fitness, relative work rate or catecholamine response between the groups [105]. Based on this, this study also provided insights into the effects of cortisol on the immune system. Both groups exhibited an increase of granulocytes after the exercise bout, whereas the lymphocyte counts of cortisol non-responders returned to baseline and the cortisol responders exhibited a significant lymphopenia [105]. Further it has been described that cortisol induces and maintains a neutrophilia some hours after release or administration [32, 92, 107], by binding intracellular, ligand-gated glucocorticoid receptors, expressed by virtually all nucleated cells in the human organism, including leukocytes [14, 22, 111]. Equally important is the control of pro-inflammatory cytokines and the stimulation of regulatory T-cell activity by cortisol [56, 129]. ACTH does not only stimulate the release of cortisol from the adrenal cortex but also exerts diverse effects on the immune system. The binding of ACTH to leukocytic receptors has the potential to inhibit certain immunological processes, such as the production of antibodies or interferons [54]. Owing to the fact that only one study included in the present review investigated the response of ACTH to heavy resistance exercise, its post-exercise kinetics remain unclear. From a physiological point of view, it can be assumed that ACTH reflects the activation of the hypothalamic-pituitary-adrenal axis in the wake of stressful stimuli.

Given the relatively small number of studies investigating the acute effects of exercise on BDNF, no firm conclusions can be drawn on the exercise-induced changes of the peripheral levels of BDNF. Several publications have previously reported significant releases of BDNF following both resistance [127] and aerobic exercise [59] as it has also been shown by Church et al. [13] and to a small degree also by Marston et al. [76] following a heavy resistance exercise bout. Nonetheless, the effects of resistance exercise on the BDNF levels in the circulation remain controversial, since some studies were not able to detect acute increases post-exercise [16, 26, 37]. Marston et al. [77] are therefore suggesting to consider the rest intervals, session volume and the blood samples used to quantify BDNF levels. None of the studies included in this systematic review compared the mentioned training parameters using heavy loading protocols. However, when comparing the heavy resistance exercise protocols employed in both studies by Marston et al. [76, 77], the one with the lower session volume (100 total repetitions per session) elicited a change of +3% [123] while serum BDNF decreased in the higher volume protocol (175 total repetitions per session) by 1% [77]. Still, it is advised to be cautious when comparing results of different studies given the different measurement contexts. From the discussed studies, it cannot be inferred that heavy resistance exercise bout-induced changes of BDNF are subject to a specific response pattern. Additionally, it can neither be confirmed nor ruled out that individual subject characteristics or training parameter influence the acute response to heavy resistance exercise.

As a member of the neurotrophin family, BDNF is described to have neuroprotective effects and to enhance neuroplasticity [78]. In this role it contributes largely to the exercise-induced improvements in cognitive domains. Beyond that, BDNF engages in immunoregulatory processes by binding the tyrosine kinase B (TrkB) and p75 neurotrophin receptors (NTR) expressed by immune cells [5, 125]. Evidence accumulates that upon binding, BDNF serves as an anti-apoptotic survival factor for B- and T-cells [125]. It was for example demonstrated that the B-cell development in the bone marrow is impaired in BDNF deficient mice, resulting in reduced number of B-cells in the peripheral blood [102] and that blocking BDNF through monoclonal antibodies increased the apoptosis rate of B-cells in vitro [25]. Additionally, it has been reported that BDNF alters the expression of cytokine mRNA in T-cells, modulating the secretion of IL-4, TNF-α and TGF-β [57]. Furthermore, by promoting the proliferation of glial cells, BDNF affects the first line of the cellular immune defense in the central nervous system [53]. Although the influence of BDNF on immune cells is now widely acknowledged, its role in the immunoregulation after exercise remains elusive. The fact that endurance exercise stress at maximal exertion but not at a moderate intensity upregulated the expression of p75 NTR on peripheral blood mononuclear cells (PBMC) could indicate that a certain intensity threshold needs to be reached in order to convey the reported effects in the context of exercise [7].

Similar to other reviews, there were no studies identified through the systematic literature search that investigated the

acute effects of heavy resistance exercise on acetylcholine, VIP, CGRP, substance p, serotonin, NGF or GDNF. The biomarkers discussed in this review were likely investigated because of their well-recognized involvement in the anabolic and catabolic adaptions following resistance exercise. Especially, biomarkers associated with parasympathetic and sensory nervous pathways might however be of less interest in strength and conditioning research, because they do not drive major muscular adaptions. Furthermore, their blood concentrations might be below the level that allows the detection of clinically relevant changes with conventional sampling methods [55].

Combining the findings of the present review and the discussed evidence regarding the effects of the selected biomarkers on the immune system in the context of exercise, it can be summarized that resistance exercise leads to transient changes in the activity of some pathways, whereby a divergent humoral milieu is created. Consequently, changes in immune system function that have been discussed for each biomarker are likely to occur. However, since the biomarkers are part of an orchestrated stress response, their impact on the immune system should not only be seen in an isolated way.

The general immunological adaptions to exercise have been documented many times during and following endurance exercise. The first response of the cellular department is characterized by a rapid mobilization of leukocytes into the blood stream (leukocytosis) [87]. Leukocyte counts, especially of neutrophils and lymphocytes, are reported to increase up to fivefold after endurance exercise stress [107]. The extent to which lymphocyte subsets are mobilized is dependent on the differential expression of adrenergic receptors on the cell surface, which underpins the significance of adrenaline and noradrenaline in the initial immune response. Accordingly, lymphocytes with an increased cytotoxic effector function such as NK-cells and CD8+ T-cells are preferentially redeployed [11, 107]. Conversely, subtypes in an early maturation stage or with limited cytotoxicity such as B-cells and CD4+ T-cells are less frequently mobilized [107]. Besides that, the magnitude of this response is dependent on exercise program variables such as intensity and duration. High intensity interval training or cycling sprints have been documented to cause greater cellular immune responses than continuous endurance exercise [51, 121]. Likewise, when intensities are matched, exercise bouts of longer duration cause greater leukocyte increases [80]. During the first hour of recovery, a fast reduction of circulating lymphocytes below the baseline has been documented, while neutrophil counts remain elevated [107], a phenomenon that is attributed to the time-lagged release of cortisol into the bloodstream [32, 92, 107]. Besides the adaptions of the cellular immune department, acute endurance exercise causes transient increases of circulating pro- (IL-1β, IL-6, TNF-α) and anti-inflammatory (IL-1ra, IL-10) cytokines [84, 116].

Even though the immunological adaptions to resistance exercise are not as extensively documented, there is evidence accumulating that they show a similar pattern to that observable following endurance exercise. It is a consistent finding across studies investigating the acute immunological response to resistance exercise in young to middle-aged subjects that total leukocyte counts increase immediately after the termination of the bout [8, 28, 86, 98, 106, 109]. Simonson et al. [106] for example demonstrated a biphasic immune regulation in response to a session of 8 x 8-10 repetitions at an intensity of 75% 1RM. The total leukocyte count and all measured subpopulations, except for basophils and eosinophils, increased following exercise, with NK-cells demonstrating the greatest increments. Subsequently, only neutrophils did not return to baseline levels by 30 minutes post-exercise [106]. In line with these findings, it was additionally reported that leukocytes, neutrophils and monocytes reached their maximum circulating levels two hours after the termination of the exercise bout [98] and that the levels of leukocytes and monocytes were still reduced 24 hours post-exercise [8].

Beyond that, the literature suggests that the acute immunological regulation in response to resistance exercise is impacted by program variables. Ihalainen et al. [48] demonstrated that the exercise stimulus must be of a certain length to cause immunological adaptions. Accordingly, leukocytosis occurred delayed following 15 sets of one repetition (MAX) compared to 5 sets of 10 repetitions (HYP) of leg press and lymphocytes did not increase at all following MAX [48]. Likewise, it was reported that a one-minute inter-set rest interval causes a significantly greater leukocytosis than a three-minute rest at the same total work [79].

It is however uncertain if, next to the general pattern and direction of the immunological adaptions to resistance exercise, the magnitude of these effects is also comparable to endurance exercise. To the author's knowledge only two studies have investigated this question and compared both exercise modes directly. Subjects that participated in a study comparing the cellular immune response to either 50 minutes of cycling or resistance exercise exhibited a leukocytosis, lymphocytosis and neutrophilia following both protocols. Yet, the alterations were greater in response to the endurance exercise bout for all immune cell subpopulations investigated [101]. These results were in line with a previously conducted study displaying a comparable experimental design [85].

Finally, considering the frequently stressed importance of catecholamines in the mobilization of immune cells and the consistently reported increase of catecholamines across studies in the present review, it is reasonable to assume that the initial immune response following a bout a heavy resistance exercise is characterized by a redistribution of leukocytes from storage sites. The release of cortisol in response to resistance exercise has previously been associated with a lymphocytopenia and maintained neutrophilia during recovery. In particular, a negative correlation of cortisol with T-helper cell counts has been reported 30 and 60 minutes after a submaximal resistance exercise session [98]. Reflecting the inconsistent results of the studies included in the present review regarding cortisol, it must be assumed that its effects on the immune system are only transmitted once an intensity threshold is reached and maintained for a sufficient period of time. Consequently, the redistribution of immune cells and their maintenance in the circulation appears to be significantly influenced by the ratio of cortisol and catecholamines [32]. The specific immunoregulatory effects that BDNF exerts in the context of exercise remain to be determined. The upregulation of BDNF-specific receptors after exercise on PBMC [7] however gives a strong indication that BDNF might not only be associated with enhanced neuroplasticity and neuroprotection post-exercise but also with "immunoprotection".

CONCLUSIONS

The present review showed that a bout of heavy resistance exercise alters the activity of specific pathways of neuroendocrine-immune regulation. Specifically, it leads to considerable increases in the peripheral concentrations of adrenaline, noradrenaline and GH immediately after the termination of the exercise bout. The reported changes in cortisol levels showed less homogeneous results and appear to be more sensitive to the configuration of the exercise scheme or individual subject characteristics.

The limited number of studies and their mixed results allow no firm conclusions to be drawn about the direction of the effect of heavy resistance exercise on the circulating BDNF and ACTH levels.

The duration of the rest periods between the sets seems to be the most influential factor for the magnitude of the response of cortisol and GH, as shorter rest periods tended to elicit greater changes. Men lean towards greater catecholamines increases than women.

Overall, the investigated biomarkers tended to return to baseline one hour after the termination of the exercise bout, albeit the recovery of cortisol showed no clear pattern. Notably, catecholamine levels exhibited the fastest recovery.

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Conflict of interest

The authors declare that there is no conflict of interest associated with the publication of this systematic review.

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