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The influence of endocannabinoids on the runner's high in humans

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Exercise-induced euphoria and anxiolysis do not depend on endogenous opioids in humans

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ABSTRACT

A runner's high describes a sense of well-being during endurance exercise characterized by euphoria and anxiolysis. It has been a widespread belief that the release of endogenous opioids, such as endorphins, underlie a runner's high. However, exercise leads to the release of two classes of rewarding molecules, endocannabinoids (eCBs) and opioids. In mice, we have shown that core features of a runner's high depend on cannabinoid receptors but not opioid receptors. In the present study, we aimed to corroborate in humans that endorphins do not play a significant role in the underlying mechanism of a runner's high. Thus, we investigated whether the development of two core features of a runner's high, euphoria and reduced anxiety levels, depend on opioid signaling by using the opioid receptor antagonist naltrexone (NAL) in a double-blind, randomized, placebo (PLA)-controlled experiment. Participants (N = 63) exhibited increased euphoria and decreased anxiety after 45 min of running (RUN) on a treadmill in a moderate-intensity range compared to walking (WALK). RUN led to higher plasma levels of the eCBs anandamide (AEA) and 2-arachidonoglycerol (2-AG). Opioid blockade did not prevent the development of euphoria and reduced anxiety as well as elevation of eCB levels following exercise. Moreover, the fraction of participants reporting a subjective runner's high was comparable in the NAL and PLA-treated group. Therefore, this study indicates that the development of a runner's high does not depend on opioid signaling in humans, but makes eCBs strong candidates in humans, as previously shown in mice.

1. Introduction

Some long-distance runners experience a runner's high as a sudden and ephemeral phenomenon during and after endurance exercise. The core features of a runner's high are euphoria, reduced anxiety, hypoalgesia, and sedation. Historically, a runner's high was believed to be related to endorphin release during running based on increased plasma levels of endorphins after running (Colt et al., 1981). Yet, even though this view gained widespread acceptance, recent findings challenge the role of endogenous opioids in core features of a runner's high and suggest an involvement of endocannabinoids (eCBs) (Dietrich and McDaniel, 2004). Both classes of molecules, eCBs and endorphins, are observed to be increased following long-distance running (Colt et al., 1981; Sparling et al., 2003). While opioids such as endorphins cannot cross the blood-brain barrier because of their hydrophilic structure, lipophilic eCBs easily penetrate the brain and are excellent candidates to explain exercise-brain interactions (Dietrich and McDaniel, 2004; Pardridge et al., 1990). In addition, various studies failed to find a correlation between positive mood effects and peripheral endorphin levels (Farrell et al., 1986; Kraemer et al., 1989; Markoff et al., 1982), while a correlation of peripheral eCBs has been found after and during exercise (Brellenthin et al., 2017; Raichlen et al., 2012).

It is still under debate whether two core features of a runner's high in human beings, euphoria and reduced anxiety, depend on endogenous opioids and/or eCBs. During exercise, a role of central opioid release has been suggested as a mechanism underlying exercise-induced euphoria

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based on an inverse correlation between opioid binding and euphoria ratings in two positron emission tomography studies (Boecker et al., 2008; Saanijoki et al., 2018a). Interestingly, however, euphoria as well as increased eCBs levels both seem to show an inversed U-shaped relation with exercise intensity, peaking at moderate intensities (Berger and Owen, 1998; Reed and Ones, 2006; Yeung, 1996) and depending on individual factors and duration (Ekkekakis et al., 2011). To our knowledge, no study has yet investigated whether opioid blockade abolishes the rise of euphoria following exercise. Thus, it is still unclear if the mechanism of exercise-induced euphoria depends on opioid release or may indeed depend on eCBs.

In mice, we have shown that anxiolysis following endurance exercise depends on intact cannabinoid receptor 1 (CB1) function on forebrain GABAergic neurons (Fuss et al., 2015). In contrast, opioid blockade did not affect anxiety-related behaviors following exercise in mice. While the anxiolytic effect of a single bout of exercise is also a robust finding in humans, both in meta-analyses (Ensari et al., 2015; Petruzzello et al., 1991) and in behavioral studies (Lago et al., 2018), our findings of an opioid-independent mechanism have not yet been corroborated in humans.

In contrast, however, an opioid-independent mechanism for exercise-induced hypoalgesia has been demonstrated across species (Crombie et al., 2018; Fuss et al., 2015; Koltyn et al., 2014). Even though strong opioid signaling was related to exercise-induced hypoalgesia (Tour et al., 2017), blockade of opioid receptors did not prevent the development of exercise-induced hypoalgesia (Crombie et al., 2018; Fuss et al., 2015; Koltyn et al., 2014) in contrast to blockade of CB1 and CB2 receptors (Fuss et al., 2015). Thus, analgesic effects during endurance exercise depend on eCB signaling, while the fourth feature, sedation, seems to be an unspecific consequence of exercise that requires neither opioid nor eCB signaling (Fuss et al., 2015).

In the present study, we aimed to investigate whether a runner's high is related to eCB and/or opioid release in humans. We focused on two core features, euphoria and anxiety, corresponding to our experimental approach in mice. Sixty-three healthy participants that regularly perform endurance exercise took part in two conditions, running (RUN) and walking (WALK). They randomly received either the central opioid blocker naltrexone (NAL) or a placebo (PLA). In contrast to rodent studies, pharmacological blockade of cannabinoid receptors is no longer available since rimonabant, the only CB1/CB2 blocker approved for human use, has been withdrawn from the market (Sam et al., 2011). Euphoria was rated before and after running/walking, and anxiety was assessed using a human elevated plus-maze (EPM), which is sensitive to anxiogenic and anxiolytic compounds (Biedermann et al., 2017). Thus, we aimed to assess a comparable approach-avoidance conflict as in mice to show cross-species validity of our earlier findings (Fuss et al., 2015). Based on the rodent data, we hypothesized that opioid antagonism would not prevent the development of a runner's high.

2. Materials and methods

2.1. Participants

Sixty-four healthy adults (32 women and 32 men) that regularly perform endurance exercise were recruited for this study. Participants were between 18 and 50 years and without a history of severe psychiatric or somatic disorders. They were invited to participate through various means, including posters in running shops and at often frequented running places, a notice on a popular website of biomedical research, and word of mouth. Inclusion criteria were performing endurance exercise more than twice a week as well as fluently speaking and reading German. Exercise habits were assessed using the International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003). Exclusion criteria were psychiatric or somatic disorders, pregnancy or breastfeeding, and any drug use in the last four weeks except contraceptive medication or prescription free medication with at least one week since the previous intake. Before attending the study, all participants completed a telephone interview ruling out exclusion criteria. Participants were asked to refrain from drinking and eating for at least two hours before arriving at the laboratory. Furthermore, they had to refrain from caffeine and nicotine intake and abstain from physical exercise on the day of testing. They were informed that we would rule out drug use using a urine drug screen. On completion of the study, participants were paid €100. The local ethics committee approved this study (Ärztekammer Hamburg, Germany).

2.2. Study procedure

All participants were invited to the laboratory twice. One male individual could not attend the second day and was thus excluded from further analyses. Participants were randomly assigned to receive either 50 mg of the opioid receptor antagonist NAL (Desitin Arzneimittel GmbH, Germany) (n = 32, men=16, women=16; BMI=22.4 ± 0.5; age=28.1 ± 1.1) or an identical-looking PLA (n = 31, men = 15, women = 16; BMI = 22.3 ± 0.4; age=26.5 ± 1.0) on both days. The dose of NAL was comparable to earlier studies in exercising individuals (Crombie et al., 2018; Koltyn et al., 2014; Strassman et al., 1989). All participants performed two different conditions, endurance running and regular walking on a treadmill, on two days with at least 30 days between both conditions. The order of the conditions was randomly assigned (n = 32 performed endurance running first). All studies were performed between 1 pm and 8 pm to minimize circadian rhythmicity on hormonal release (Hanlon et al., 2015). During the entire study, individuals could drink water ad libitum.

On day 1, after ruling out exclusion criteria, participants gave informed consent. Subsequently, a urine test screening for amphetamine, benzodiazepine, cocaine, morphine, methadone, and cannabis use was performed (Multi-6 Drogentest, Diagnostik Nord, Germany). Following negative results, participants took 50 mg of NAL or an identically looking PLA prepared by a person not involved with the study.

Afterward, participants completed the short version of the IPAQ, the Acrophobia Questionnaire (AQ) (Cohen, 1977), the Spielberger State-Trait Anxiety Inventory (trait part) (STAI) (Spielberger et al., 1999), and the Sensation Seeking Scale Form V (SSS-V) (Zuckerman et al., 1978). Furthermore, sociodemographic information was collected using a self-constructed questionnaire asking for age, sex, somatic and psychiatric problems, medication, drug consumption, experiences with virtual reality, exercise-related behaviors, and socioeconomic factors. Undesirable side effects were assessed 50 min after intake of NAL/PLA addressing dry mouth, dry skin, blurred vision, dullness, nausea, vertigo, headaches, and restlessness on a 7-item scale (not existent, barely existent, existent, moderate, strong, really strong, extreme) using a self-designed scale (Table S1a and S1b).

Subsequently, participants were asked to make slash marks at ten visual analog scales (VAS) on a horizontal line indicating their emotional state (confusion, anger, sadness, happiness, sedation, energy, anxiety, tension, euphoria, and feeling of dejection from 0 (no) to 100 (high) (Table S2)(Boecker et al., 2008)).

Next, blood samples were collected, and participants performed the RUN or WALK condition for 50 min on a treadmill. The performance was monitored using the individual age-adjusted maximum heart rate (AAMHR) of participants (Tanaka et al., 2001). Earlier research showed that eCB levels peak at an AAMHR between 70% and 85%, describing moderate-intensity under the lactate threshold (Raichlen et al., 2013). Participants in the RUN condition exercised in this range. The equation '*208–0.7 * age*' was used to calculate the maximum heart rate (Tanaka et al., 2001). In the WALK condition, individuals were asked to walk below 50% of their AAMHR. Heart rate was monitored using a TomTom Runner 2 device, which gave a signal whenever participants exceeded or fell below their targeted heart rate zone. In the running condition, individuals could warm up five minutes before running 45 min in their calculated heart rate zone. After endurance exercise or walking for 45

min, participants again indicated their emotions on 10 VAS scales and blood was sampled as described below. Next, anxiety was assessed using a human version of the elevated plus-maze (EPM) in a virtual reality environment. The investigation ended with a questionnaire asking participants whether they had experienced a runner's high in the laboratory (yes/ no/ I do not know).

2.3. Blood sampling

Blood was sampled before and after exercise, at the dominant hand when possible. To ensure a minimal contribution of circadian eCB level variation (Hillard, 2018), blood was collected between 2 pm and 7 pm. Stasis time was kept below one minute to avoid hemolysis. Plasma was collected using a 7.5-mL tube coated with ethylenediaminetetraacetic acid (Monovette; Sarstedt AG & Co, Münbrecht, Germany) and immediately transferred to a cooled centrifuge in the same room. Samples were centrifuged for ten minutes at a force of 2000 x g and a temperature of 4° Celsius. Plasma was sampled immediately, aliquoted, and stored at − 85 °C until further analyses.

2.4. Endocannabinoid measurement

ECBs, the eCB-like molecule palmitoyl ethanolamide (PEA), and arachidonic acid (AA) were extracted from 100-μL plasma samples and measured according to the protocol previously described (Post et al., 2020; Lerner et al., 2019; Lerner et al., 2018). Plasma eCB levels were normalized to the plasma volume using the following formula:

% change in plasma volume = (100/[100 Hct pre]) 100([Hct pre - Hct post]/Hct post* (van Beaumont, 1972).

Because of missing hematocrit values, eight samples in the RUN condition (PLA: n = 4; NAL: n = 4), and six samples in the WALK condition (PLA: n = 5; NAL: n = 1) could not be normalized using hematocrit adjustment.

2.5. Human elevated plus-maze

The human EPM is a behavioral test to assess anxiety on a subjective and behavioral level in a standardized aversive environment. The task has been validated and is sensitive to anxiogenic and anxiolytic compounds (Biedermann et al., 2017). The human EPM consists of a real-world wooden maze combined with a maze representation in virtual reality. The real-world maze consists of four wooden arms (width 30 cm, height 20 cm) placed in the room's middle. Each arm has a length of 175 cm, covering in total 350 × 350 cm, within an experimental room (550 × 550 cm) with two virtual reality tracking systems (HTC Vive Base Station®, Seattle, USA) attached at 250 cm height on opposite walls. Participants entered the room with closed eyes and were guided by one of the experimenters towards the maze. Next, they received a headset (HTC Vive®, Seattle, USA), noise-canceling headphones (Bose QuietComfort 35®, Framingham, USA) and were instructed to open their eyes. After checking the participant's vision in a baseline graphical environment, the virtual reality software (A+ cross®, VirtualRealWorlds.com, Germany) was started. Participants found themselves in a 550 × 550 cm large virtual room with a virtual wooden plus-maze (350 × 350 cm) in front of them. Importantly, the virtual reality plus-maze and the real-world physical plus-maze had the same shape, material, and size as well as position in the virtual and real world. A recorded voice instructed participants to step on the maze and walk slowly towards the maze center, where they had to wait for 60 s to allow for baseline measurements. Further, they were instructed that they would be allowed to explore the environment on the maze once the scene had changed. The behavioral experiment started after 90 s and participants found themselves in a new environment. In the new scenario, only the virtual plus-maze remained unchanged. Instead of being in a virtual room, the maze was placed on day one on a virtual rocky mountain surrounded by water. Two opposite arms (here termed closed arms as in the rodent EPM) and the maze center were surrounded by rocks, while the other arms reached out over the water, which was roughly 55 m below (open arms). On day 2, the maze was placed on rocks above an icy landscape with a strong wind from ahead and several cars on the ground that was again roughly 55 m below the maze. Open arms were also unprotected, while virtual rocks sheltered closed arms. Simultaneously, with the virtual environment change, two fans were started in the experimental room to increase the perception of being present in the virtual environment. The fans were placed at the end of the arm that participants were initially facing to give the impression of cool wind from ahead. Participants could explore the EPM for 300 s. After the scenario ended, they removed their headsets and left the room with closed eyes.

They rated their anxiety level on the EPM on a scale from 0 (no anxiety) to 9 (very strong anxiety). Moreover, we asked for side effects and other emotions (such as 'having panic,' on a scale from 0 (not at all) to 9 (very strongly)) (Table S3). Additionally, behavioral measures were recorded on the virtual reality computer as well as an external hard drive. However, behavioral data were lost following a break-in into our virtual reality laboratory.

2.6. Statistical analyses

Statistical analyses were carried out using IBM SPSS Statistics 23.0 (IBM Corp., Armonk, USA). ECBs and euphoria levels were assessed using a two-way repeated measures ANOVA with time (PRE vs. POST) x condition (RUN vs. WALK) as within-subject variables and drug treatment (NAL vs. PLA) as between-subjects factor. For heart rate, a two-way repeated measures ANOVA with time (15 time intervals: 0–3 min, 3–6 min, 6–9 min…42–45 min) x condition (RUN vs. WALK) as within-subject variables and drug treatment (NAL vs. PLA) as between-subjects factor was used. Assessing anxiety levels on the elevated plus-maze, a repeated measures ANOVA with condition (RUN vs. WALK) as within-subject variable and drug treatment (NAL vs. PLA) as between-subjects factor was used. For this ANOVA, we also added sex as cofactor and age as a covariate as our earlier research had shown that sex and age both influence anxiety on the human EPM (Biedermann et al., 2017). A chi-square test of independence (2 × 3) was used to compare the number of those that experienced a runner's high under laboratory conditions between NAL and PLA. All data are given as mean ± standard error (SEM). Statistical significance was set at $p < 0.05$, and effect sizes are given as η_p^2 for ANOVAs.

3. Results

Most participants (81%) reported performing high levels of physical activity at baseline with comparable levels between both groups (PLA: n = 24 (77%) high, n = 7 (23%) moderate; NAL: n = 27 (87%) high, n = 5 (13%) moderate physical activity levels in IPAQ). Moreover, participants also reported comparable levels of trait anxiety (STAI: PLA=33 ± 1, NAL=35 ± 2), sensation seeking (SSSV: PLA = 63 ± 1, NAL=63 ± 1) and acrophobia (AQ: PLA = 15 ± 3, NAL = 12 ± 2) at baseline (Table 1).

3.1. Endocannabinoid release in response to endurance exercise and walking

Both conditions (RUN and WALK) stimulated an increase of eCB plasma levels. There was a main effect of time for the eCBs anandamide (AEA) and 2-arachidonoglycerol (2-AG) as well as the eCB-like molecule palmitoylethanolamide (PEA) and arachidonic acid (AA) (AEA: $F_{1,59}$ =150.66, $p < 0.001$, $\eta_p^2 = 0.719$; 2-AG: $F_{1,61} = 35.34$, $p < 0.001$, $\eta_p^2 = 0.367$; PEA: $F_{1,61} = 163.22$, $p < 0.001$, $\eta_p^2 = 0.728$; AA: $F_{1,61} = 139.67$, $p < 0.001$, $\eta_p^2 = 0.696$). Moreover, RUN led to a stronger increase reflected by a main effect of condition (AEA: $F_{1,59}$ =18.95, $p < 0.001$, η_p^2 =0.243; 2-AG: $F_{1,61} = 3.00$, $p = 0.088$, $\eta_p^2 = 0.047$; PEA: $F_{1,61} = 9.43$, $p = 0.003$, $\eta_p^2 = 0.134$; AA: $F_{1,61} = 23.14$, $p < 0.001$, $\eta_p^2 = 0.275$) and a time*

Table 1
Sample description: Sensation Seeking Scale Form V + (SSSV), Acrophobia Questionnaire (AQ), Spielberger State-Trait Anxiety Inventory (STAI), International Physical Activity Questionnaire (IPAQ).

	Placebo	Naltrexone
Participants (n)	31 (f = 16, m = 15)	32 (f = 16, m = 16)
BMI (kg/m²)	22.26 (SEM ± 0.4)	22.39 (SEM ± 0.5)
Age	26.52 (SEM ± 1.0)	28.06 (SEM ± 1.1)
SSS-V sum score	63.07 (SEM ± 1,2)	63.31 (SEM ± 0.9)
AQ sum score	14.76 (SEM ± 2.9)	12.23 (SEM ± 1.8)
STAI sum score (trait part)	32.83 (SEM ± 1.1)	35.07 (SEM ± 1.6)
Physical activity levels (IPAQ)		
Low	0	0
Moderate	7	5
High	24	27
Did you experience a runner's high during RUN?		
Yes	5	7
No	20	19
I do not know	6	6
Did you ever experience a runner's high before?		
Yes	23	21
No	3	4
I do not know	5	7

condition interaction (AEA: $F_{1,59} = 26.80$, $p < 0.001$, $\eta_p^2 = 0.312$; 2-AG: $F_{1,61} = 8.91$, $p = 0.004$, $\eta_p^2 = 0.127$; PEA: $F_{1,61} = 17.00$, $p < 0.001$, $\eta_p^2 = 0.218$; AA: $F_{1,61} = 30.21$, $p < 0.001$, $\eta_p^2 = 0.331$). Descriptively, the increase of plasma levels was roughly two-fold higher in the RUN compared to the WALK condition (AEA: +91% vs. +48%, 2-AG: +43% vs. +14%, PEA: +63% vs. +38%, AA: +210% vs. +120%) (Fig. 1).

NAL treatment did not influence eCB release as there was no main drug treatment effect (all $p > 0.1$). As expected, heart rate was higher in the RUN condition ($F_{1,60} = 1690.70$, $p < 0.001$, $\eta_p^2 = 0.966$) and increased over time ($F_{1,60} = 33.51$, $p < 0.001$, $\eta_p^2 = 0.358$). A time * condition interaction revealed that the heart rate under RUN conditions showed a more pronounced increase ($F_{1,60} = 9.09$, $p = 0.004$, $\eta_p^2 = 0.132$). NAL treatment did not affect heart rates ($p > 0.1$).

3.2. Core features of a runner's high are not affected by opioid antagonism

We were interested in how two core features (euphoria, reduced anxiety) of a runner's high are affected by opioid antagonism during running. Euphoria levels roughly doubled in the RUN condition, while they remained virtually unchanged in the WALK condition. This was reflected by a main effect of time ($F_{1,57} = 19.91$, $p < 0.001$, $\eta_p^2 = 0.259$), condition ($F_{1,57} = 18.62$, $p < 0.001$, $\eta_p^2 = 0.246$) as well as time * condition interaction ($F_{1,57} = 30.49$, $p < 0.001$, $\eta_p^2 = 0.348$) (Fig. 2).

NAL treatment did not affect the rise of euphoria levels in runners ($p > 0.1$). After RUN, participants also experienced less anxiety when subjected to an elevated plus-maze task, reflected by the condition's main effect ($F_{1,57} = 5.40$, $p = 0.024$, $\eta_p^2 = 0.086$). Again, NAL treatment did not prevent the reduction of anxiety after RUN ($p > 0.1$).

3.3. Experiencing a runner's high under laboratory conditions

Most participants reported to have experienced previously a runner's high (70%; PLA: 74%, NAL: 66%). From these, 33% in the NAL and 22% in the PLA group reported a runner's high under our laboratory conditions during RUN. While participants in the NAL group had thus descriptively a higher likelihood to experience a runner's high, this difference was not significant ($\chi^2(1) = 0.74$, $p = 0.39$). Only one participant experienced a runner's high in the WALK condition (PLA: $n = 1$). Interestingly, this individual showed an increase of AEA (+76%), 2-AG (+63%), PEA (+126%), and AA (+83%) comparable to the RUN condition.

4. Discussion

In the present study, we demonstrate that opioid blockade had no significant influence on reducing subjective anxiety or the rise of euphoria rendering a crucial role for endogenous opioids and particularly endorphins unlikely. However, the study provides evidence that a runner's high depends on eCBs by demonstrating a rise of eCB levels accompanied by an increase of euphoria and reduced anxiety levels following endurance exercise.

Two aspects have been essential for producing beneficial effects related to a runner's high in clinical trials, intensity and duration. Performing sports under the anaerobic threshold seems to be an excellent trigger to produce those sudden pleasant feelings of euphoria, anxiolysis, sedation, and analgesia (Brellenthin et al., 2017; Raichlen et al., 2013). Furthermore, the positive effects of aerobic exercise on mood appear after 30–35 min (Reed and Ones, 2006). Both factors depend on each other so that limited duration can be compensated by higher intensities and vice versa (Basso and Suzuki, 2017). Studies that lack a specific duration and/or intensity frequently create inconsistent findings (Ekkekakis et al., 2011; Reed and Ones, 2006).

Higher intensity and duration were also connected to the opioid system signaling in positron emission tomography. For example, Saanijoki et al. (2018b) found decreases of μ-opioid receptors-selective radioligand binding in frontolimbic brain regions after high-intensity interval training. The decreased binding was associated with negative

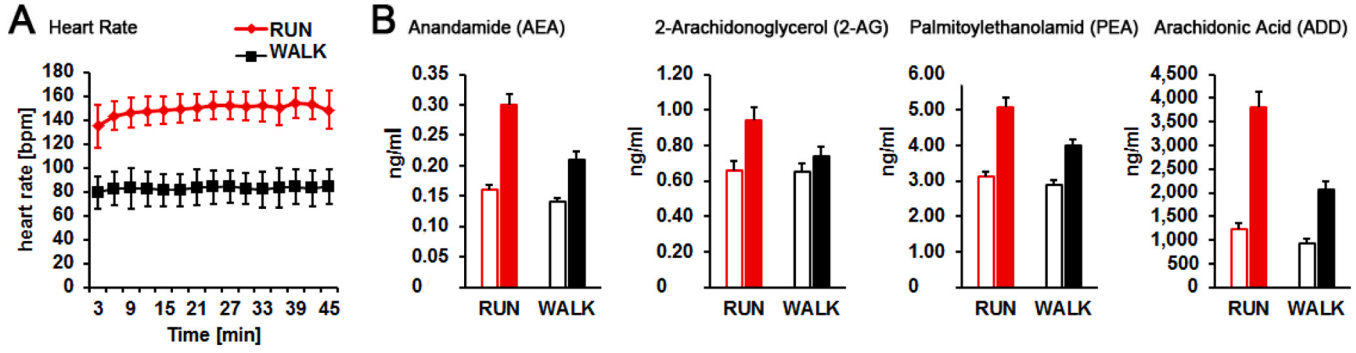

Fig. 1. A. Heart rate in RUN compared to WALK condition (N = 63). Means are depicted ± SEM. B. Both eCBs (AEA and 2-AG), as well as PEA and AA, showed an increase after WALK and RUN; however, the increase was roughly double-fold in the RUN condition. Left open columns represent $Mean_{pre}$ + SEM and solid (red and black) columns $Mean_{post}$ + SEM (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

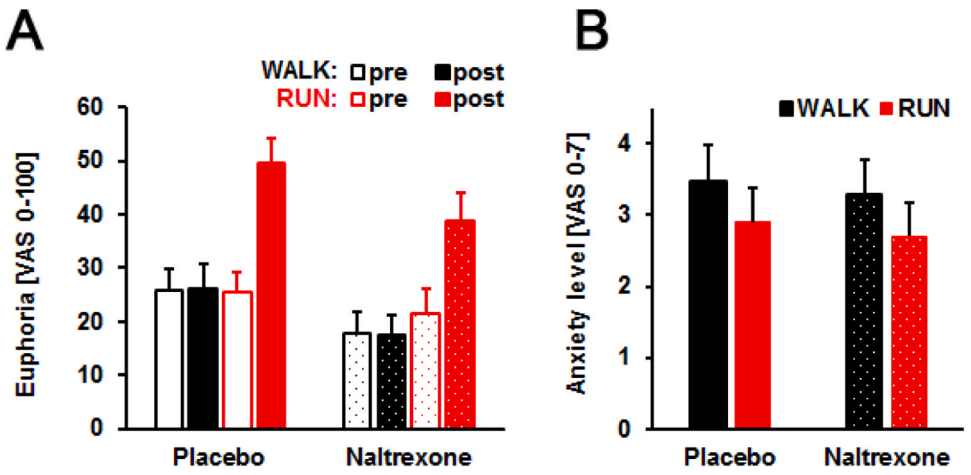

Fig. 2. A. Euphoria levels increase in the RUN compared to WALK condition in the PLA (n = 31) and NAL-treated (n = 32) group. Means are depicted ± SEM. B. Anxiety levels on the human elevated plus-maze are lower after RUN compared to WALK in both groups (NAL vs. PLA). Columns represent Means + SEM.

mood. In comparison, 60 min of moderate-intensity cycling did not alter μ-opioid receptors binding and increased euphoria. Furthermore, after two hours of endurance running, Boecker et al. (2008) found decreased binding of a non-selective opioidergic ligand in frontolimbic brain regions, which correlated inversely with euphoria. While these findings leave the door open for the possibility that the opioid system may play a role in higher intensity or prolonged endurance exercise, the current findings strongly argue against a prominent role for endogenous opioids in the development of a runner's high.

4.1. The rise of endocannabinoids during endurance exercise

Interestingly, while earlier studies with smaller sample size found an increase of eCB levels only after endurance exercise with an AAMHR between 70% and 85% (Raichlen et al., 2013), we found that eCB levels were also, albeit less strongly, increased in our control condition when participants walked on a treadmill with an AAMHR below 50%. Intriguingly, the one participant who even reported a subjective runner's high during the walking condition was found to have an increase of plasma eCBs during walking that was roughly comparable to the average increase in the RUN condition. This result is in line with earlier reports finding an increase of eCB levels following hiking (Feuerecker et al., 2012), masturbating (Fuss et al., 2017), or singing (Stone et al., 2018). Thus, it appears that positive consequences of eCB release may appear after different rewarding behaviors that stimulate eCB release. So far, however, it is not clear whether eCBs have to exceed a certain threshold level to have a biologically meaningful effect on mood and behavior or whether this effect is rather regulated on a continuum where increasing levels are related to increasing impacts. On the one hand, our data support the latter explanation. Most of our participants did not report to have experienced what they understand as a '*runner's high*' under our laboratory conditions. Nevertheless, we were able to find a small-to-medium effect of treadmill running on anxiety and a medium-to-large effect on euphoria levels compared to walking. We hypothesize that if we had chosen a different control condition that does not stimulate eCB release, these effects might have been even more extensive. On the other hand, participants in the WALK condition did not report a rise in euphoria levels even though eCBs were released in this condition. The latter point suggests a threshold level that needs to be exceeded so that eCBs lead to euphoria development.

4.2. Future directions to elucidate the role of endocannabinoids and endorphins in endurance exercise

It would be interesting to compare the plasma level increase of eCBs from our study to those of people experiencing a runner's high under naturalistic conditions. Based on some of our participants' subjective reports that indicated having experienced a runner's high before, certain contextual factors also play a crucial role in the development of a runner's high such as listening to music, watching a beautiful landscape, or having emotional thoughts. Future research should address these contextual factors to understand if they might have an additive effect on eCB release or facilitate the development of a runner's high through additional mechanisms.

While we have shown in the present study that acute exercise increases eCBs, the long-term consequences of repeated stimulation of the eCB system in regularly exercising humans have not yet been investigated sufficiently. For example, decreased 2-AG plasma levels were found in humans after an 80-day aerobic and strength exercise intervention (Koay et al., 2020). Similarly, we found a negative correlation between the daily voluntary running distance and plasma levels of the eCB anandamide after nine weeks of exercise in mice (Biedermann et al., 2016). These data indicate that repeated stimulation of the eCB system may have long-term consequences on eCB levels that have insufficiently been studied in humans yet. It was also shown that CB1 receptors control rodent voluntary running performance in VTA GABAergic terminals (Dubreucq et al., 2013), highlighting a potential role for eCBs in motivational aspects of regular endurance exercise.

We performed a urine drug screen with all participants on both days of testing, ruling out prior recreational cannabis use since we were concerned that cannabis use might interfere with the eCB system. However, in recent years, a growing number of popular media (Miller, 2018; Hesse, 2016) report about long-distance runners using cannabis to facilitate achieving a runner's high. Future research should investigate this phenomenon, e.g., by examining how exogenous cannabinoids affect eCB release as well as mood and behavior.

4.3. Limitations and future directions in the research of a runner's high

Our results concerning the core aspects of a runner's high are in line with our findings in mice (Fuss et al., 2015) and provide mounting evidence for an essential role of eCBs in the biological mechanisms of anxiety and euphoria (Dubreucq et al., 2015; Lutz et al., 2015). Thus, the beneficial consequences of acute exercise seem to be a conserved mechanism depending on eCB release across species. However, the major limitation of the present study is that we could not block cannabinoid receptors, as there is currently no CB1-receptor blocker available for use in humans. Therefore, while we found no significant effect of opioid blockade, we hypothesize that CB1-receptor blockade would prevent the development of a runner's high in humans comparable to

our findings in mice (Fuss et al., 2015).

Furthermore, it is essential to be aware of the involvement of various other signaling pathways during exercise. For example, neurochemicals (lactate, cortisol, catecholamines) and neurotransmitters (serotonin, dopamine) are also involved in exercise-related mood changes (Basso and Suzuki, 2017). For example, serotonin as well as dopamine receptors are colocalized with CB1 receptors on neurons in various brain regions (Hermann et al., 2002) and both neurotransmitter systems are affected by exercise and play a major role in anxiety regulation as well as reward processing (Flack et al., 2019; Fuss et al., 2013). Thus, various pathways are intertwined making it demanding to understand the intricate orchestration of involved molecules.

The next steps in the study of the runner's high should ideally be to combine different theories and systems that can explain aspects of a runner's high. Thus, a unified theory of a runner's high should be developed, ranging from molecules to brain regions to behavior. In particular, the link with neuroimaging data could be fruitful in understanding the role of endocannabinoids in the deactivation of the prefrontal cortex that occurs after acute exercise and could explain some of the emotional and behavioral effects linking the hypofrontality and endocannabinoid theories (Dietrich, 2003; Dietrich and Audiffren, 2011).

However, research into a runner's high is methodologically demanding. While it can be beneficial to identify and best control the effects of exercise under laboratory conditions, our study also shows that the sterile laboratory environment may be detrimental for the development of such ephemeral phenomena as a runner's high. Only few people reported the subjective experience of a runner's high under our laboratory conditions compared to those reporting having had one previously. A more naturalistic setting with contextual factors supporting the development of a runner's high may be helpful in future research if the focus is on achieving a higher number of participants reporting a runner's high. Meanwhile, controlled and standardized laboratory conditions may be beneficial if the focus is on having comparable conditions across groups and avoiding external confounders.

5. Conclusion

In conclusion, this study corroborates our findings in mice that opioid blockade does not prevent positive effects of acute exercise and shows that euphoria, which could not be studied in mice, does not seem to depend on endorphins.

Author contributions

Michael Siebers, Sarah V. Biedermann and Johannes Fuss designed the study, analyzed the data, and wrote the first draft of the manuscript. Michael Siebers collected data. Laura Bindila and Beat Lutz performed the endocannabinoid measurement and contributed to preparation of the manuscript. All authors commented on and approved the final manuscript.

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Competing interests

The authors declare no competing interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2021.105173.

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Do Endocannabinoids Cause the Runner's High? Evidence and Open Questions

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Abstract

The runner's high is an ephemeral feeling some humans experience during and after endurance exercise. Recent evidence in mice suggests that a runner's high depends on the release of endocannabinoids (eCBs) during exercise. However, little is known under what circumstances eCBs are released during exercise in humans. This systematic review sampled all data from clinical trials in humans on eCB levels following exercise from the discovery of eCBs until April 20, 2021. PubMed/NCBI, Ovid MEDLINE, and Cochrane library were searched systematically and reviewed following the PRISMA guidelines. From 278 records, 21 met the inclusion criteria. After acute exercise, 14 of 17 studies detected an increase in eCBs. In contrast, after a period of long-term endurance exercise, four articles described a decrease in eCBs. Even though several studies demonstrated an association between eCB levels and features of the runner's high, reliable proof of the involvement of eCBs in the runner's high in humans has not yet been achieved due to methodological hurdles. In this review, we suggest how to advance the study of the influence of eCBs on the beneficial effects of exercise and provide recommendations on how endocannabinoid release is most likely to occur under laboratory conditions.

Keywords

endocannabinoid, runner's high, exercise, euphoria, endurance, running

Introduction

The search for the neurobiological causes of the runner's high has fascinated scientists and laymen for the past decades. A runner's high is defined as an emotional state during or after endurance training characterized by reduced pain sensitivity, sedation, euphoria, and reduced anxiety. Some have also emphasized a lost sense of time and feelings of effortlessness (Dietrich and Audiffren 2011).

Historically, studies of the 1980s (Appenzeller 1981; Carr and others 1981) claimed that the release of endorphins, a hydrophilic molecule binding to opioid receptors, is responsible for the runner's high. The endorphin hypothesis was poorly supported by evidence, although it was widely perpetrated by the media (Dietrich and McDaniel 2004). Several findings speak against this hypothesis: First, peripheral endorphins do not have a major effect on the brain, as they cannot cross the blood-brain barrier due to their hydrophilic structure (Dietrich and McDaniel 2004). In line, a connection between peripheral endorphin levels during endurance exercise and elevated mood could not be found (Kraemer and others 1989). Second, blockage of the opioid system did not affect the subjective experience during endurance exercise (Farrell and others 1986; Markoff and others 1982).

In the 1990s, two main endogenous endocannabinoids (eCBs) were discovered: arachidonoyl ethanolamide, which was termed "anandamide" (AEA) in 1992 (Devane and others 1992), and 2-arachidonoyl glycerol (2-AG) in 1995 (Mechoulam and others 1995). Their discovery led to the so-called endocannabinoid hypothesis of the runner's high. In comparison to endorphins, eCBs are lipophilic molecules and can penetrate the blood-brain barrier easily, making them better candidates to explain the runner's high (Dietrich and McDaniel 2004; Fuss and others 2015; Siebers and others 2021; Watkins 2018). The eCB system is a potent endogenous system involved in various physiological functions in the nervous system. Some

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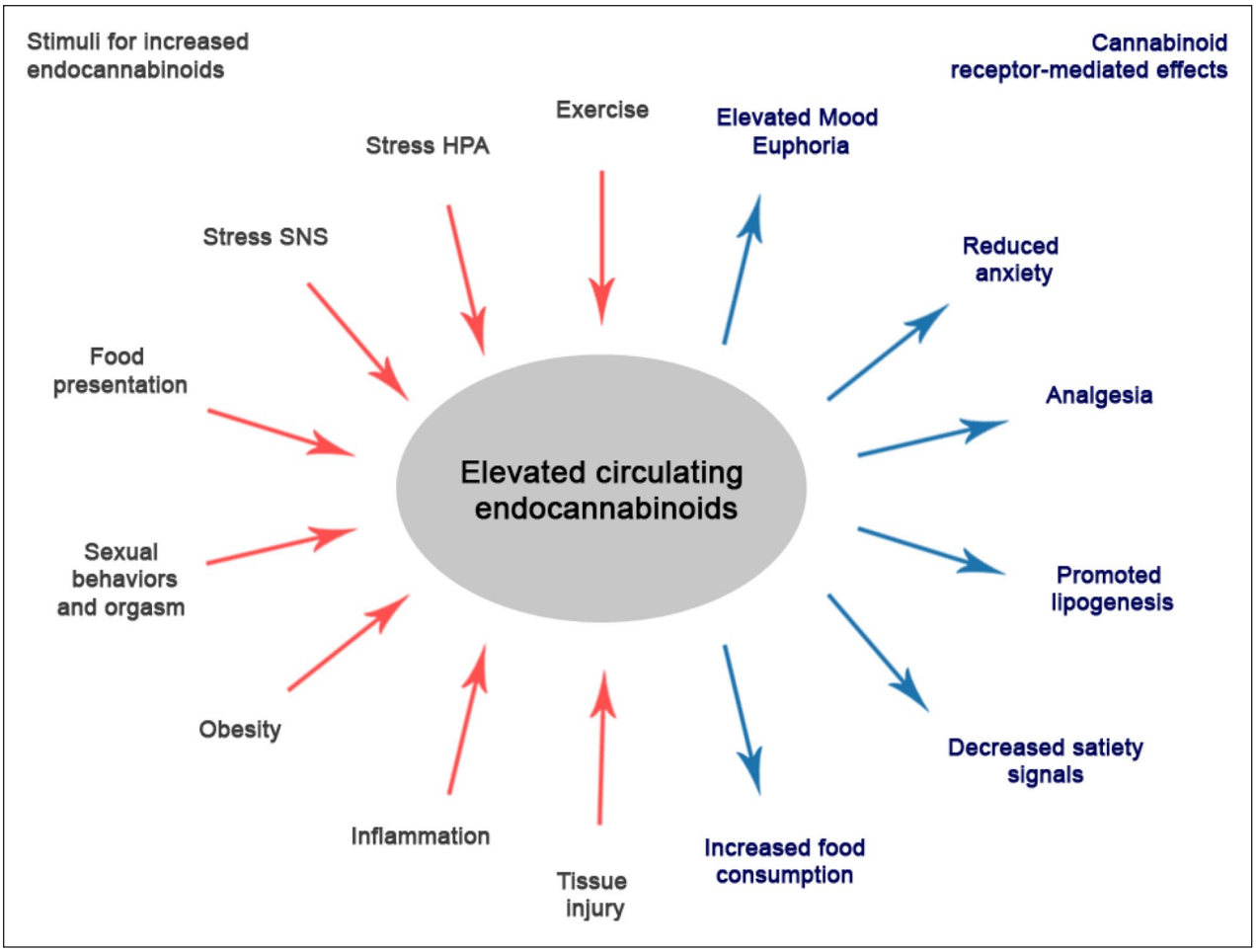

Figure 1. The release of endocannabinoids is triggered by various stimuli (red arrows). Higher levels of endocannabinoids in turn were associated with a plethora of (neuro)biological consequences (blue arrows). The figure is adapted and updated from Hillard (2018).

involved physiological processes are synaptic transmission, mood, reward, anxiety, appetite, memory processing, neuroprotection, and neuroinflammation (Hillard 2018; Watkins 2018; Fig. 1). Furthermore, they also play important roles during neural development, for example, neuronal proliferation, neuronal migration, and axonal growth (Hillard 2015). The two main eCB compounds, AEA and 2-AG, bind to G-protein-coupled cannabinoid receptors CB1 and CB2. In addition, various related biogenic lipids are often described and sampled in addition to the eCBs since they involve the same precursors, such as N-acylated ethanolamine phospholipids (N-oleoylethanolamine [OEA], N-palmitoylethanolamine [PEA], N-stearoylethanolamine [SEA]) and diacylglycerol (2-oleoylglycerol [2-OG]).

Interestingly, it seems that not every human can experience a runner's high. For example, studies with endurance runners reported that only 69% to 77% of the participants experienced a runner's high at least once in the past (Hinton and Taylor 1986; Siebers and others 2021). This finding may however also stem from a poor conceptualization of the runner's high as participants are usually only asked whether they ever experienced this phenomenon without further description. This complicates research into the neurobiology of a runner's high.

Despite the inconsistent occurrence in humans, the neurobiological basis of the endophenotypes of the runner's high can be studied in animal models. Various studies indicated that eCB signaling is essential for voluntary wheel running in mice and rats (Dubreucq and others 2010; Dubreucq and others 2013; Fuss and others 2015; Galdino and others 2014). Studies also showed that two criteria of the runner's high, hypoalgesia and anxiolysis, were indeed related to an increase in eCBs postexercise in animal models (Fuss and others 2015). However, another aspect of the runner's high, euphoria, is yet not possible to study in animal models. Therefore, in recent years, there have been increasing efforts to investigate the relationship between characteristics of the runner's high and

eCBs in humans. This systematic review aims to provide a contemporary overview of the relation between endurance exercise and eCBs, and also addresses the four main features of the runner's high: reduced pain sensitivity, sedation, euphoria, and reduced anxiety.

Method

A systematic search for trials concerning endurance exercise and the eCB system was conducted in accordance with the PRISMA guidelines (Shamseer and others 2015).

Inclusion Criteria

All trials that met the following criteria were included: (1) published in English in a peer-reviewed journal; (2) original article; (3) experimental trials with human participants; (4) containing aerobic exercise, namely, cycling, running, or hiking; (5) with a duration of at least 20 minutes; (6) low- to high-intensity levels; (7) measurement of eCB and eCB-like lipid levels in the blood before and after exercise or comparing eCBs in an exercise and control group.

Procedure

To provide an overview of studies regarding eCBs and the runner's high, a keyword list was defined (endocannabinoid AND (running OR cycling OR hiking OR exercise OR physical activity)). First, PubMed/NCBI and Ovid MEDLINE, and Cochrane library were checked systematically until April 20, 2021. The Mesh Terms "Exercise" and "Endocannabinoids" were used if possible. For example, the following search was used in PubMed: ("Exercise"[Mesh]) AND ("Endocannabinoids"[Mesh]).

The list was complemented by studies from past reviews and personal libraries. First, by reading the titles and, if necessary, by reading the abstracts, all studies were ordered into two groups: animal studies and human studies by two independent reviewers (Fig. 2). Next, every unique article was examined to determine whether the studies follow the inclusion criteria by reading the abstracts. Especially, attention was paid to the criteria of time series eCB and eCB-like lipids comparison in blood and endurance exercise. After the articles' discard, 35 studies met inclusion criteria and were further analyzed. In the end, 21 articles met the inclusion criteria with 31 samples (26 on acute exercise; 5 on long-term exercise). The studies were ordered alphabetically in two tables regarding acute exercise (Table 1) or long-term exercise training (Table 2) including 571 participants (243 women, 306 men, 22 not reported). In total, this systematic research included 378 participants in the study of acute exercise and 193 individuals who were studied regarding long-term exercise training. Nineteen of the 378 and 46 of the 193 participants did not perform exercise as they were part of a control group.

Results

Blood Sampling Methods and Exercise Time

Most of the articles focused on eCB blood levels before and after acute exercise (81%; Table 1). More than half of the studies observed eCB levels after exercise on a treadmill (57%) followed by cycling (29%). Only one study examined eCB levels during hiking in nature (Feuerecker and others 2012). In general, participants were performing exercise from 20 to 60 minutes (warm-up and cool-down excluded; see Tables 1 and 2) with an average time of 37 minutes. Mostly, blood was sampled before and immediately after acute exercise. One study measured eCBs in blood serum (Meyer and others 2019), whereas all other studies measured eCBs in blood plasma. Two studies sampled only blood after a break of more than 10 minutes after exercise (Cedernaes and others 2016; Stensson and Grimby-Ekman 2019). Articles that studied chronic exercise sampled blood before and after the long-term exercise program. Nearly all included articles reported on AEA levels (95%), 76% reported on 2-AG, 43% on OEA, 48% on PEA, and one study reported on AA (arachidonic acid) or 2-OG levels in blood (5%).

Acute Exercise and AEA Levels

The rise of AEA was a robust finding after a bout of exercise across studies. Fourteen of 17 articles (82% of the articles) detected an increase in AEA after acute exercise. Four samples did not find any difference (15%), and one sample observed a decrease in AEA (4%). Participants performed moderate-intensity exercise described as 70% to 85% of the age-adjusted maximum heart rate (AAMHR) in seven of the 17 studies and were controlled by a less intense condition (e.g., walking on a treadmill $<$50% AAMHR, or remaining seated for the same time). All studies with a control group described an increase in AEA compared to the control condition.

Acute Exercise and 2-AG Levels

The impact of acute exercise on 2-AG levels was less consistent. Five of 14 articles (12 of 23 samples; 52%) found an increase of 2-AG after acute exercise, and eight of 14 articles demonstrated no changes (11 of 23 samples; 48%). In six of the 14 studies, participants performed moderate-intensity exercise and were controlled by a less intense condition. Only two studies described an increase in 2-AG compared to the control condition.

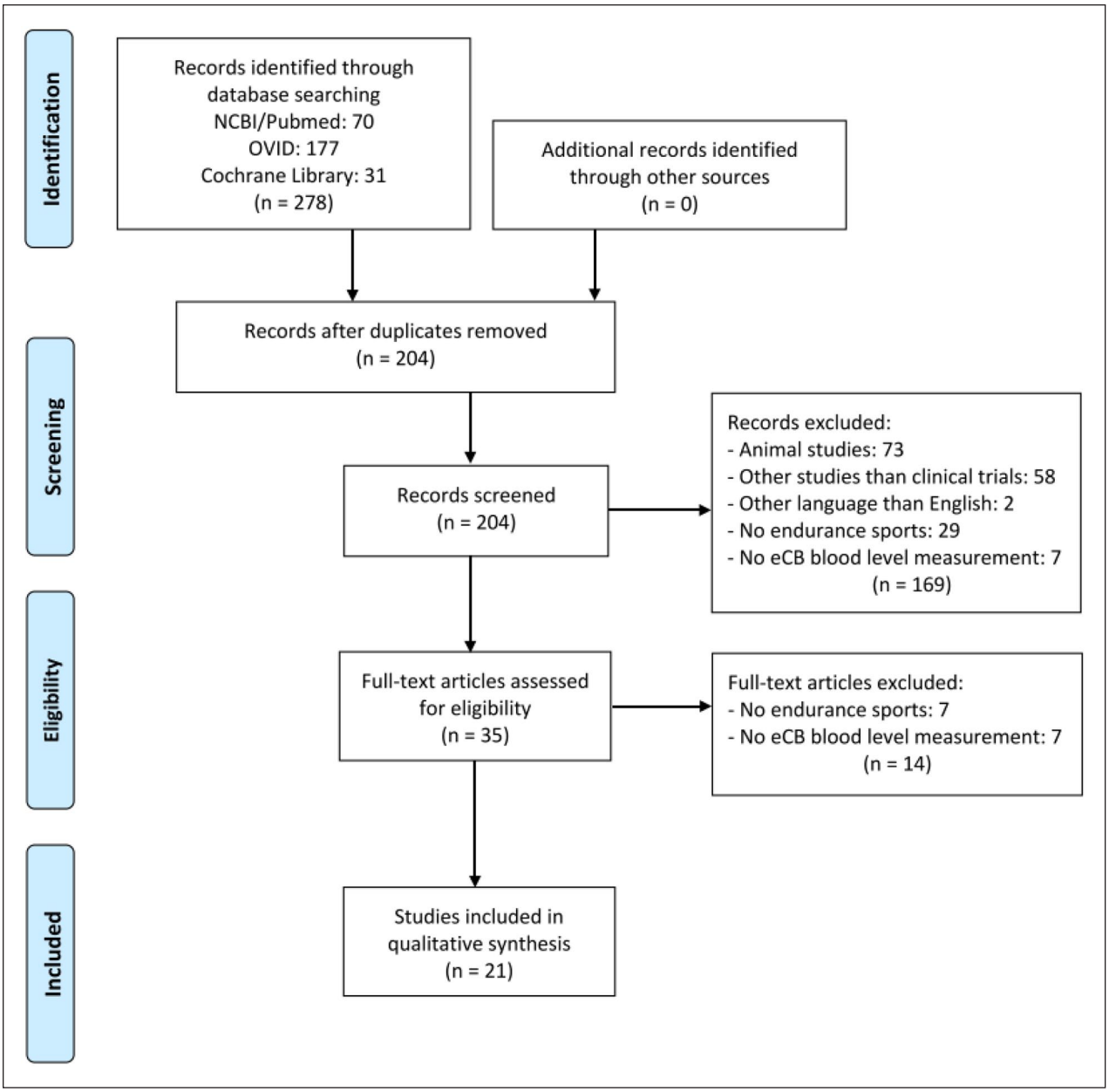

Figure 2. Flow chart of literature search including all steps performed according to the PRISMA statement (Moher and others 2009).

Acute Exercise and Other eCB-Like Molecules

Seven of 10 studies (13 of 17 samples; 76%) found an increase in OEA after exercise, but only four of 10 studies (9 of 19 samples; 47%) found an increase in PEA. Furthermore, one study detected no change of 2-OG after exercise, and one study observed an increase in AA after exercise. Just two studies contained a moderate intensity and were controlled by a less intense condition. Both studies described an increase in OEA, PEA, or AA in comparison to the control condition.

Long-Term Endurance Exercise and eCBs

All four studies regarding exercise programs of at least 12 weeks detected a decrease in the eCBs studied, namely, AEA (3 studies; 100%) or 2-AG (2 studies; 100%). There were no measurements of other eCB-like molecules.

Anxiolytic Effects after Sport

Eight of 14 acute exercise studies and two of four long-term exercise studies observed changes in anxiety using

Table 1. Studies Regarding Acute exercise.

Investigators	Participants (n)	**Average Age (in Years)**	Primary Exercise Stimulus	Exercise Intensity	Additional Warm-Up and Cool-Down	Control Condition	Blood Sampling	Further Detecting Methods	Time Main Effect of Postexercise Blood Levels			Further Outcomes
									AEA	2-AG	Other eCB	
Antunes and others (2016)	n = 18 physically active men (aerobic exercise 5×/week) divided into a group with symptoms of sports addiction (SA, n = 8) and CON (n = 10)	SA: 32.9 ± 4.7 CON: 30.2 ± 3.1	60 minutes of running on a treadmill after 2 weeks of exercise deprivation period	Ventilatory threshold	NA	NA	At baseline, after 7 days of exercise deprivation, after 14 days of exercise deprivation, and postexercise	Q: POMS (version Brunel) at the same time-points as blood sampling. Negative Addiction Scale and Exercise Dependence Scale were questioned at the first visit	↑* only in CON	NA	NA	AEA was decreased significantly at all time points in SA compared to CON and did not increase after the exercise. Depressive mood symptoms, fatigue, confusion, anger, and vigor loss increased in SA during withdrawal. There was a mood improvement after training in SA. No significant mood changes were detected in CON at all time points.
Marin Bosch and others (2020)	n = 15 healthy and recreational fit male participants (VO_{2max} above 40 mL/kg/min and below 65 mL/kg/min)	23.7 ± 4	45 minutes cycling on an ergometer (30 minutes at a moderate intensity and 15 minutes at a high intensity)	Moderate intensity: 70% AAMHR corresponding to 60% $VO2_{max}$ High intensity: 80% AAMHR corresponding to 70% VO_{2max}	3 minutes warm-up; 3 minutes cool-down	30 minutes resting	Before and after exercise/resting	Q: STAI, questionnaires for depression, and circadian typology M: A serial reaction time task before and after the condition, and an fMRI analysis 45 minutes after the condition	↑#	NA	NA	AEA increased significantly after moderate and high intensity in comparison with resting. High-intensity exercise increased the motor sequence memory significantly and a trend was visible for moderate-intensity exercise. The increase in motor sequence memory correlated with AEA expansion and coincided with local expansions in caudate nucleus and hippocampus activity.
Brellenthin and others (2017)	n = 36 healthy adults (18 women and 18 men) divided into three groups after their weekly physical activity (low: n = 11, moderate: n = 12, and high: n = 13)	21.1 ± 3.8	45 minutes running on a treadmill	70% to 75% VO_{2max}	10 minutes warm-up	45 minutes running on a treadmill at preferred intensity and time	Before and after exercise	Q: PAR at the beginning POMS, STAI, CES before and after running	↑*	↑#	OEA: ↑* PEA: ↑#	AEA and OEA increases were higher in prescribed running ($P < 0.05$). There were significant decreases in tension ($P < 0.05$), depression ($P < 0.01$), anger ($P < 0.05$), TMD ($P < 0.05$), and increases in vigor ($P < 0.01$) after both exercise conditions. The decrease in state anxiety, TMD, and confusion was greater in the preferred condition ($P < 0.05$).
Brellenthin and others (2019)	n = 21 participants (12 men; 9 women) with substance use disorder divided into two groups: intensive outpatient treatment (IOP; n = 10) or IOP plus aerobic exercise treatment (IOP-EX; n = 11)	IOP: 35.0 ± 7.1 IOP-EX: 35.1 ± 0.2	6 weeks IOP plus exercise (30 minutes incline walking on a treadmill 3 times a week)	Rising intensities from the first 3 weeks from 65% to 70% till the last 3 weeks at an intensity of 75% of AAMHR	5 minutes warm-up	IOP with 30 minutes sitting on a chair three times a week	Once a week before and after exercise or sitting	Q: POMS, Craving Questionnaires–Short Forms before and after treatment once a week after exercise or sitting PHQ-9, GAD-7, SCQ, and PSS asked at baseline and after 6 weeks of treatment	↑# only in IOP-EX (NR long-term effects of exercise)	↔ (NR long-term effects of exercise)	NA	Both treatments reduced perceived stress ($P < 0.01$), craving, tension, depression, anger, confusion, and TMD (all $Ps < 0.05$). The exercise group experienced acute increases in vigor.
Cedernaes and others (2016)	n = 16 healthy men with a regular sleep rhythm of 7–9 hours	22.9 ± 0.7	30 minutes ergometer cycling after three nights of sleep restriction (4.25-hour sleep opportunity)	Cycling: 75% of the VO_2 reserve capacity	5 minutes warm-up	30 minutes of ergometer cycling after three nights of normal sleep (8.5-hour sleep opportunity)	At five time points: day 3 at 7:30 p.m.; day 4 at 8:30 a.m., ~10 a.m. (pretreatment), ~15 minutes postexercise, and ~4 hours postexercise	NA	↔	↑* only after 8.5 hours sleep and only after 15 minutes postexercise	OEA: ↑# (only after 4 hours postexercise) PEA: ↔	NA

(continued)

Table 1. (continued)

Investigators	Participants (n)	**Average Age (in Years)**	Primary Exercise Stimulus	Exercise Intensity	Additional Warm-Up and Cool-Down	Control Condition	Blood Sampling	Further Detecting Methods	Time Main Effect of Postexercise Blood Levels			Further Outcomes
									AEA	2-AG	Other eCB	
Crombie and others (2018)	n = 24 participants (6 men, 18 women) divided into PTSD (n = 12; 3 men, 9 women) and CON (n = 12; 3 men, 9 women)	25.0 ± 5.6	30 minutes running or walking on a treadmill	70% to 75% AAMHR	10 minutes warm-up	NA	Before and after exercise	Q: POMS, STAI, PANAS, MPQ-SF before and after running	↑#	↑*	OEA: ↑* PEA: ↔ 2-OG: ↔	Pain decreased after running ($P = 0.001$). State anxiety, negative affect, tension, fatigue, confusion, and TMD were reduced (all $Ps = 0.001$ to 0.050). Higher reductions in negative mood states occurred after exercise in the PTSD group than in the control group.
Crombie and others (2019)	n = 20 participants (5 men, 15 women) divided into PTSD (n = 10) and CON (n = 10)	23.7 ± 7.2	30 minutes running or walking on a treadmill	70% to 75% AAMHR	5 minutes warm-up 5 minutes cool-down	The Trier Social Stress Test (TSST)	Before and after exercise/TSST	Q: Before and after running/TSS, POMS, STAI, PANAS	↑#	↑* only in CON	OEA: ↑# PEA: ↔	Vigor ($P = 0.023$) and positive affect ($P = 0.038$) were increased after running. There were significant group × time interactions for tension ($P = 0.025$), depression ($P = 0.040$), fatigue ($P = 0.005$), confusion ($P = 0.023$), TMD ($P = 0.05$), state anxiety ($P = 0.05$), and negative affect ($P = 0.05$) with general reduction in the PTSD group after running. AEA increased after the TSST.
Crombie and others (2020)	n = 40 trauma-free women (n = 12), trauma-exposed women without PTSD (n = 14), and trauma-exposed women with PTSD (n = 14)	24.1 ± 6.0	30 minutes running or walking on a treadmill	70% to 75% AAMHR	5 minutes warm-up 5 minutes cool-down	40 minutes sitting	Before and after exercise/resting	Q: Before and after running/ resting POMS, STAI, PANAS; RPE every 5 min during exercise; after Neutral-Predictable-Unpredictable threat task (NPU) AFRQ M: after exercise/ resting NPU	↑#	↑#	OEA: ↑# PEA: ↑#	Anxiety and fear ratings to NPU were significantly lower following exercise compared to resting ($P < 0.05$). Participants with higher increases in peripheral sampled eCBs had higher reductions in anxiety and fear ratings to NPU following exercise. There were significant reductions in fatigue, confusion, TMD, and increases in positive affect after exercise in all groups ($Ps < 0.05$). A significant postexercise increase in all eCBs ($Ps < 0.05$) was measured in comparison to sitting.
Feuerecker and others (2012)	n = 12 young healthy men	27.6; range: 24–38	Protocol A (PA): physical exercise at a lower altitude Protocol B (PB): physical exercise by an active ascent to high altitude	NR	NA	Protocol C (PC): passive ascent by a helicopter	Before the start, at the summit cottage 60 to 90 minutes upon arrival, in the morning after the overnight stay, and 60 to 90 minutes after returning to base camp the next day	NA	↑* only in PA and PB	↔	NA	A more pronounced increase was found under high-altitude conditions in PB. PC demonstrated no significant eCB level changes.
Heyman and others (2012)	n = 11 young well-trained male cyclists	23.3 ± 5.1	60 minutes pedaling on an ergometer followed by a 30-minute intense endurance performance test (TT)	55% of W_{max}, and TT with a known endpoint equal to 30 minutes at 75% of W_{max}	NA	NA	Before exercise, after 15 minutes sitting, after 60 minutes constant pedaling, after the end of the exercise, and 15 minutes after recovery	NA	↑* only after TT	↔	OEA: ↑# after 60 minutes ↑# after TT PEA: ↑* after 60 minutes ↑# after TT	AEA did not increase significantly after 60 minutes pedaling at an intensity of 55% W_{max}. Cortisol increased at TT and recovery in comparison to baseline ($Ps < 0.001$). AEA correlated positively with cortisol. AEA, OEA and PEA were significantly higher after 15 minutes of recovery compared to the end of the exercise.

(continued)

Table 1. (continued)

Investigators	Participants (n)	**Average Age (in Years)**	Primary Exercise Stimulus	Exercise Intensity	Additional Warm-Up and Cool-Down	Control Condition	Blood Sampling	Further Detecting Methods	Time Main Effect of Postexercise Blood Levels			Further Outcomes
									AEA	2-AG	Other eCB	
Meyer and others (2019)	n = 17 women with mayor depressive disorder	40.8 ± 14.8	20 minutes prescribed ergometer cycling (PRI)	Intensity of 13 rated on the RPE	5 minutes warm-up 5 minutes cool-down	20 minutes of ergometer cycling with preferred intensity (PRE)	Serum before and within 10 minutes postexercise	Q: POMS, STAI before, 10 and 30 minutes postexercise; RPE every 5 minutes during exercise	↑* only in PRI	↔	OEA:↑* only in PRI PEA: ↔	All subscales of the POMS ($Ps < 0.05$) and TMD ($Ps < 0.01$) were improved after exercise. STAI was just increased after PRI ($P < 0.001$). Significant negative correlations ($Ps < 0.05$) were observed 10 minutes after the PRE between AEA and depression, confusion, fatigue, TMD, and STAI. 30 minutes postexercise negative correlation between AEA and confusion, TMD, and state anxiety were detected. There were no significant associations between PRE and mood changes.
Raichlen and others (2012)	n = 10 recreationally fit humans, 8 mixed-breed dogs, and 8 ferrets	NR	30 minutes running on a treadmill	70% to 80% of AAMHR	NA	30 minutes of walking calculated by Froude number	Before and after treatment	Q: PANAS before and after treatment	↑*	↔	NA	Pre- and postpositive affect of the PANAS was positively correlated to the increase in AEA in humans.
Raichlen and others (2013)	n = 10 healthy regular runners (6 men and 4 women)	31.9 ± 12.1	30 minutes running on a treadmill on four different days	Four different intensities: (I) HR < 50% AAMHR (II) HR ~ 70% AAMHR (III) HR ~ 80% AAMHR (IV) HR ~ 90% AAMHR	NA	Walking on a treadmill (I)	Before and after treatment	NA	↑* only in II and III	↔	NA	NA
Siebers and others (2021)	n = 63 recreationally active participants (32 female; 31 male) divided into a placebo (n = 31) and a naltrexone group (50 mg; n = 32)	Placebo group: 26.5 ± 1.0 Naltrexone group: 28.1 ± 1.1	45 minutes running on a treadmill	Running at a moderate-intensity of 70% to 85% AAMHR	5 minutes warm-up	45 minutes of walking on a treadmill with an intensity less than 50% of AAMHR	Before and after treatment	Q: STAI, VAS, IPAQ, AQ, Anxiety VAS after Human Elevated plus-maze M: Human Elevated plus-maze	↑#	↑#	PEA: ↑# Arachidonic acid: ↑#	Endorphin blockade by naltrexone did not inhibit eCB release, anxiolytic effects, or euphoria after running. Euphoria was nearly twofold higher after running but remained roughly unchanged after walking. Anxiolytic effects were observed after the run condition ($P = 0.024$).

(continued)

Table 1. (continued)

Investigators	Participants (n)	**Average Age (in Years)**	Primary Exercise Stimulus	Exercise Intensity	Additional Warm-Up and Cool-Down	Control Condition	Blood Sampling	Further Detecting Methods	Time Main Effect of Postexercise Blood Levels			Further Outcomes
									AEA	2-AG	Other eCB	
Sparling and others (2003)	n = 24 male athletes divided into a group of running (R; n = 8), a group of cycling (C; n = 8), and CON (n = 8)	23.7 ± 9.4	45 minutes running or cycling	70% to 80% AAMHR	5 minutes warm-up	50 minutes of resting seated	Before and after treatment	N/A	↑# after R ↑* after C	↔	NA	Plasma levels of 2-AG showed a similar trend during sports, but not in sedentary controls.
Stensson and Grimby-Ekman (2019)	n = 32 participants (22 women, 10 men) divided into a group with chronic neck pain (CNP; n = 21) and CON (n = 11)	CNP: 50.8 ± 12.9 CON: 37.7 ± 15.9	30 minutes dynamic arm cycling	Increasing load and a steady pace of 25 laps/min	NA	NA	Before and 60 minutes after arm cycling	M: PPT using a handheld electronic pressure algometer and rated on a numeric rating scale before, immediately after, and 60 minutes after arm cycling	↓* only in CON ↔ only in CNP	↔	OEA: ↔ PEA: ↔	Pain intensity demonstrated no statistically significant change during the whole study.
Stone and others (2018)	n = 9 women (mean 61 years) recruited from a local choir	61; range 55–67	30 minutes cycling (n = 8) performed in a group activity	NR	NA	30 minutes of dancing, reading, singing performed in a group activity on various dates	Before and after activity	Q: PANAS before and after activity	↔	NA	OEA:↑* PEA: ↔	AEA, OEA (*Ps* < 0.05), and PEA (*P* < 0.01) increased after singing significantly. There was a significant improvement in positive mood and emotions after singing (*Ps* < 0.01). All activities included, OEA was correlated with positive mood effects (*P* = 0.0025). Cycling had no impact on mood rating.

CON = control group; NA = not applicable; NR = not reported; Q = questionnaires; M = further measurements; AEA = anandamide; 2-AG = 2-arachidonoyl glycerol; OEA = oleoylethanolamine; PEA = palmitoylethanolamine; 2-OG = 2-oleoylglycerol; SEA = stearoylethanolamide; POMS = Profile of Mood States; AQ = Acrophobia Questionnaire; IPAQ = International Physical Activity Questionnaire; TMD = Total Mood Disturbance; PANAS = Positive and Negative Affect Schedule; STAI = State-Trait Anxiety Inventory; AFRQ = Anxiety and Fear Rating Questionnaire; PAR = Physical Activity Recall; CES = Commitment to Exercise Scale; GAD-7 = Generalized Anxiety Disorder Scale-7; MPQ-SF = Short-form McGill Pain Questionnaire; PPT = pressure-pain threshold; VAS = visual analog scale; AAMHR = age-adjusted maximum heart rate; PTSD = posttraumatic stress disorder; RPE = rate of perceived exertion.
*$P < 0.05$, #$P < 0.01$.

Table 2. Studies Regarding the Long-Term Effects of Exercise Training.

Investigators	**Participants (n)**	**Age (in Years)**	**Primary** Exercise Stimulus	**Exercise Intensity**	**Additional** Warm-Up **and** Cool-Down	**Control** Condition	**Blood** Sampling	**Other** Detecting Methods	**Time** Main Effect **of** Post**exercise** Blood Levels		**Further Outcome**
									AEA	2-AG	
Di Marzo and others (2009)	n = 49 viscerally obese men	Average age 49 years	One-year intervention of lifestyle modification program including nutrition changes and physical activity	NR	NA	NA	Before and after the 1-year lifestyle program	M: BMI and waist circumference; visceral adipose tissue (VAT) by computer tomography, and detection of triacylglycerol levels HDL_3-cholesterol in blood before and after the program.	↓#	↓#	Levels of 2-AG correlated with decreases in VAT and triacylglycerol levels and the increase in HDL_3-cholesterol levels. BMI and waist circumference decreased significantly (*Ps* < 0.0001).
Oliveira and others (2019a)	n = 34 participants (18 women, 12 men, 4 NR) divided into exercise group (n = 17) and CON (n = 17)	38 ± 11.5	12-week program of 30 minutes running or walking on a treadmill three times a week	VT	5-minute warm-up; 5-minute cool-down	Routine sports activity defined as ≤1 day/ week	Before and after 12 weeks of treatment/ control after Q	Q: POMS before and after 12 weeks of treatment/control	↓* only in the exercise group	NA	Anxiety, anger, TMD, and body weight decreased significantly in the exercise group (*Ps* < 0.05). AEA decrease was associated with weight loss.
Oliveira and others (2019b)	n = 58 participants (41 women, 9 men, 8 NR) with or without migraine divided into migraine waitlist group (n = 15), migraine exercise group (M-EX; n = 15), control exercise group (CON-EX; n = 14), and control waitlist group (n = 14)	36.2 ± 10.9	A 12-week program of 30 minutes running on a treadmill three times a week	VT	5-minute warm-up; 5-minute cool-down	Waiting list continuing routine activity	Before and after 12 weeks of treatment/ control condition after Q	Q: POMS before and after 12 weeks of treatment/control condition, neurological examination and checking of headache diaries every 4 weeks M: Cardiorespiratory fitness test at baseline and end 1 week after Q and blood sampling	↓# only in CON-EX ↓* only in M-EX	NA	The number of days with migraine (*P* < 0.01), migraine attacks (*P* < 0.05), and abortive medication used (*P* < 0.05) were decreased in the M-EX. Cardiorespiratory fitness increased in M-EX and CON-EX (*Ps* < 0.05). Anxiety, depression, anger, and fatigue scores decreased in the M-EX (*Ps* < 0.05). There was a correlation between the reduction of abortive medication used and cardiorespiratory fitness (*P* < 0.001) as well as reduced AEA (*P* < 0.05).
Koay and others (2020)	n = 52 newly enlisted male soldiers	22 ± 4	80-day exercise intervention as part of the Army Recruit Course	NR	NA	NA	Before and after the 80-day exercise intervention early in the morning	M: BMI, body fat, blood pressure, estimated VO_{2max}	NA	↓*	BMI (*P* = 0.02), body fat (*P* < 0.001), blood pressure (*P* < 0.0001) decreased. The estimated VO_2 max was increased (*P* < 0.0001) post-training intervention.

NA = not applicable; NR = not reported; CON = control group; Q = questionnaires; M = further measurements; AEA = anandamide; 2-AG = 2-arachidonoyl glycerol; POMS = Profile of Mood States; TMD = Total Mood Disturbance; VT = ventilatory threshold; BMI = body mass index.
*$P < 0.05$, #$P < 0.01$.

either a questionnaire (Profile of Mood States [POMS] = 9, 90%; State-Trait Anxiety Inventory [STAI] = 5, 50%), Neutral-Predictable-Unpredictable threat task (NPU; n = 1), or a human elevated plus-maze (n = 1). The results were inconsistent. Eight studies (80%) and 12 samples (63%) described a decrease in anxiety after acute and long-term physical activity, whereas seven samples (37%) could not find any changes. Two studies described contradicting results. Brellenthin and others (2017) described a decrease in anxiety during preferred in contrary to prescribed exercise, in contrast to Meyer and others (2019), who reported that only prescribed exercise decreased anxiety.

Positive Mood Effects after Exercise

Eleven studies assessed mood via questionnaires. Eight studies used the POMS, four the positive affect subscale of the PANAS questionnaire and one study used a visual analog scale (VAS). Twelve samples found a decrease in Total Mood Disturbance (TMD) in the POMS, three found increased positive mood in the PANAS, and one study described euphoria after exercise on a VAS. In total, nine of 11 studies (82%) and 17 of 20 samples (85%) reported a positive effect of acute exercise on mood.

Hypoalgesia after Exercise

Only two studies focused on hypoalgesia effects after exercise. The results were inconsistent. One study described less pain after exercise (Crombie and others 2018), and one study described no pain changes in a pressure-pain threshold (PPT) task after exercise (Stensson and Grimby-Ekman 2019).

Sedation after Exercise

No study researched postexercise sedation effects.

Description of Selected Studies

Acute Endurance Exercise and Endocannabinoids. The first to demonstrate that physical exercise activates the eCB system were Sparling and colleagues in 2003 (Sparling and others 2003). They studied 24 male volunteers that regularly performed endurance exercise. Those that indicated to run or cycle were also assigned to their preferred exercise regime (i.e., running or cycling, respectively) or to a control condition. Participants performed exercise in a range of 70% to 80% of maximum heart rate (140–160 bpm) for 45 minutes, whereas control subjects remained seated for 50 minutes. Sparling and others (2003) found that AEA levels significantly increased compared to controls in both exercise groups. Data for 2-AG levels were not reported in the article, but the authors stressed that 2-AG levels showed a similar trend but did not reach statistical significance.

Nine years later, Heyman and colleagues (2012) investigated 11 young, well-trained male cyclists. They used a more standardized protocol than Sparling and others (2003), allowing no exercise, alcohol, or coffee 24 hours before testing and provided a standardized breakfast. The exercise started 150 minutes after breakfast with 60 minutes pedaling at 55% of their maximal power output (W_{max}), immediately followed by a 30-minute endurance performance task at an intensity equal to 75% W_{max}. They found that AEA levels increased after intense exercise and continued to rise after recovery, while 2-AG levels remained stable throughout the experiment. Moreover, the eCB-like lipids PEA and OEA gradually increased after moderate exercise, intense exercise, and recovery. However, 60 minutes of cycling at 55% of W_{max} did not significantly increase AEA levels.

Another interesting study was performed by Raichlen and others (2012), who hypothesized that cursorial mammals and humans are equipped with a neurobiological make-up that facilitates moderate-intensity endurance exercise. They studied the eCB system's response to exercise in a cursorial mammal species (dogs), a non-cursorial species (ferrets), and humans during 30 minutes of treadmill walking or running. They found that only dogs and humans showed an increase in AEA in response to exercise, while this was absent in non-cursorial ferrets. 2-AG showed no reaction to exercise. Interestingly, changes in AEA significantly correlated with changes in the positive affect subscale of the PANAS questionnaire. Moreover, under control conditions, both eCBs remained stable. Thus, the authors concluded that humans and dogs achieve physiological and psychological improvements through exercise-induced AEA release and hypothesized that this biological mechanism is more broadly evolved in some mammalian species to provide them with the ability to run long distances.

Raichlen and others (Raichlen and others 2013) further investigated in human runners how exercise intensity affects eCB levels in a follow-up study. The 10 participants were analyzed on four different days simultaneously on a treadmill, walking or running at four different intensities for 30 minutes in random order. Interestingly, Raichlen and colleagues found that only endurance exercise at ~70% and ~80% of AAMHR significantly affected AEA levels. This suggests that neither walking-speed training nor high-intensity running affects AEA. Following their arguments, 70% to 85% of AAMHR is the perfect range to achieve a runner's high.

One study (Brellenthin and others 2017) examined the impact of mood response on prescribed or preferred

exercise among individuals with various physical activity levels per week. They invited 36 participants and categorized them into low, moderate, and high physical activity groups based on their weekly physical activity. Participants performed prescribed running for 45 minutes (70% to 75% VO_{2max}) and, on a second day, preferred running with participants' choice of intensity. Running on a treadmill in prescribed and preferred conditions increased AEA, 2-AG, OEA, and PEA significantly in all groups. Intensity of weekly physical activity did not influence mood or eCB release. However, OEA and AEA were higher in the prescribed condition. There were significant effects on tension, depression, anger, and increases in vigor after both exercise conditions in questionnaires. In comparison to the prescribed condition, state anxiety, TMD, and confusion were higher in the preferred condition.

The specific influence of the surroundings on the runner's high is not fully understood. In a less standardized paradigm, just one study (Feuerecker and others 2012) investigated in nature how hiking in the alps under hypoxic conditions affects the eCB system. Healthy young male volunteers (n = 12) performed hiking for several hours at two different altitudes. They found that AEA increases after exercise, and they discovered a more pronounced increase under high altitude conditions. However, the high altitude conditions alone did not affect AEA levels under control conditions (no-exercise) when participants were transported with a helicopter to the same altitude. Moreover, 2-AG levels were not affected by hiking.

Including a functional magnetic resonance task, the effects of exercise on motor sequence memory in brain and its correlation to AEA were studied (Marin Bosch and others 2020). In a crossover design, on three different time points, 15 participants cycled for 30 minutes at moderate intensity (70% VO_{2max}), for 15 minutes at a high intensity (80% VO_{2max}), or rested for 30 minutes. Before and after the condition, a serial reaction time task took place where participants needed to execute a sequence of keypresses with four fingers during an fMRI analysis to investigate memory for motor sequences. As a result, again, AEA increased significantly after high and moderate intensity. High-intensity cycling enhanced the motor sequence memory significantly and a trend was observed for moderate-intensity exercise. This improvement correlated with AEA increase and coincided with local expansions in caudate nucleus and hippocampus activity. For the first time, this article implies that eCBs interact with brain signaling after exercise in humans involving hippocampus-related functions.

In a double-blind, randomized within-subject study, 63 recreationally active participants received 50 mg of the opioid antagonist naltrexone or an identical-looking placebo to further clarify whether endorphins or eCBs are essential for the runner's high (Siebers and others 2021). Next, on two different dates, they ran 45 minutes at an intensity of 70% to 85% of AAMHR or walked 45 minutes (<50% AAMHR) on a treadmill. Blood samples and a VAS about the participant's emotional state were acquired directly before and after each condition. Anxiety was assessed in a human elevated plus-maze using virtual reality. All eCBs increased significantly after both conditions but were twofold higher after running (Fig. 3). Euphoria was also nearly twofold higher after running but remained roughly unchanged after walking. Moreover, anxiolytic effects were observed after running (Fig. 4). Opioid blockade did not inhibit anxiolytic effects or euphoria after running. Also, the release of eCBs was not prevented by opioid blockage after running and walking. In conclusion, this study suggests that the runner's high does not depend on endorphins (Siebers and others 2021).

It is important to emphasize that some studies did not detect an increase in AEA after exercise. Cedernaes and others (2016) were studying 16 young and healthy male volunteers who performed 30 minutes of exercise on an ergometer at 75% of VO_2 reserve capacity. The participants exercised after three nights with 8 hours sleep opportunity and, on another period, with three nights of 4.25 hours sleep opportunity. As a result, no increase in AEA, but 2-AG was found in the study. Furthermore, OEA increased significantly 4 hours postexercise with and without sleep restriction. Of note, between the termination of exercise and blood sampling was a 15-minute time gap, which may have affected the results. In contrast, after three nights of sleep restriction, the group observed no significant 2-AG release.

Moreover, in a study where 21 participants with chronic pain were compared with 11 healthy controls in 30 minutes of arm cycling with an increasing workload, no increase in eCBs was found (Stensson and Grimby-Ekman 2019). PPT was tested before, immediately, and 60 minutes after the physical activity. Pain intensity demonstrated no significant changes during all time points within both groups. Conversely, AEA was significantly decreased 60 minutes after the exercise in healthy controls. No other time-condition changes were detected in the eCB system. Importantly, the study's intensity was not focused on individual aspects, and the blood was drawn 60 minutes after the bout of exercise. Thus, the study might have analyzed the homeostatic downregulation of the eCB system.

In line, Stone and others (2018) did not detect significant AEA changes after 30 minutes of cycling in a spin class. They recruited nine women from a choir and observed AEA, OEA, and PEA in four different conditions of group activity: 30 minutes of dancing, reading, singing, or spinning. Interestingly, OEA was the only

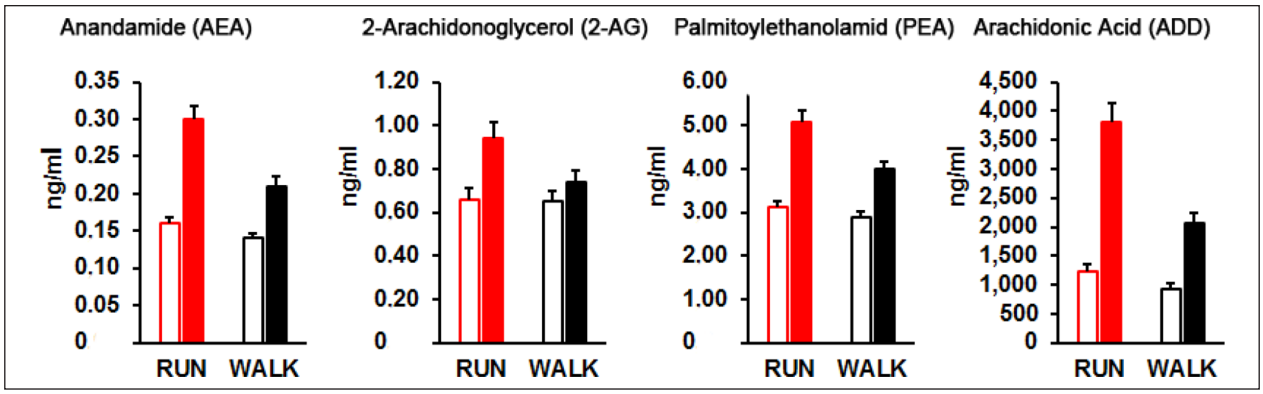

Figure 3. Moderate-intensity running (RUN) stimulates endocannabinoid-release significantly more pronounced than low-intensity walking (WALK). Left open columns represent $Mean_{pre}$ + SEM and solid (red and black) columns $Mean_{post}$ + SEM. Adapted from Siebers and others (2021).

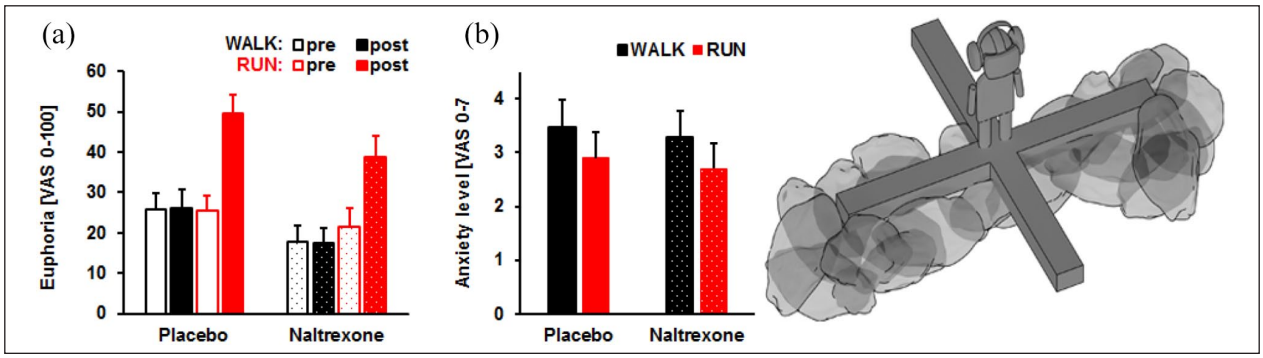

Figure 4. (A) Euphoria levels increase in the running (RUN) compared to walking (WALK) condition in the placebo (n = 31) and naltrexone-treated (n = 32) groups. (B) Anxiety levels on the human elevated plus-maze are lower after RUN compared to WALK in both groups (NAL vs. PLA). Columns represent Means + SEM. The left panels are reprinted from Siebers and others (2021), with permission from Elsevier. The right panel shows a schematic depiction of the human EPM adapted from Biedermann and others (2016).

eCB-like lipid, which increased after 30 minutes of spin class. Notably, the heart frequency measured immediately after the bout of exercise was less than the 70% AAMHR suggested by Raichlen and others (2013). One further explanation for the absence of an eCB increase might be that the eight participating women from the choir were not used to spinning class or dancing class. In contrast, the participants showed a significant increase in all measured eCBs and eCB-like substances during a regular singing class in the choir. Also, mood and positive emotions increased significantly after singing but not after cycling. Thus, this study suggests that the experience of positive emotions may somehow be necessary to release eCBs. Furthermore, the study indicates that other activities than endurance sports can activate the eCB system.

Long-Term Consequences of Exercise on the Endocannabinoid System. Less is known about the effects of long-term training on the eCB system. Koay and others (2020) studied how an 80-day exercise intervention as part of the Army Recruit Course affects various metabolic substrates. In this study, 52 young, male, and lately enlisted soldiers were included. Laboratory parameters (e.g., 2-AG), body mass index (BMI), body fat, blood pressure, and estimated VO_{2max} were measured before and after an 80-day exercise program containing moderate-intensity aerobic and strength exercise. Among various changes after the exercise program, 2-AG was 1.11-fold decreased. Furthermore, BMI, body fat, and blood pressure were reduced, and VO_{2max} was increased after the Army Recruit Course.

Compared with a control group, one study (Antunes and others 2016) found decreased AEA levels in a group of exercise addiction at all time points during a 2-week exercise deprivation period. For this trial, they invited 18 participants who regularly performed five times per week exercise and divided participants into a control group

(n = 10) and an exercise-addicted group (n = 8). Next, an exercise withdrawal for 2 weeks took place, followed by running on a treadmill for 60 minutes at ventilatory threshold intensity. Blood was sampled at baseline, after 7 days, after 14 days, and post running. Strikingly, lower AEA levels at all time points in the exercise-addicted group compared with the control group were found. Running did elevate AEA levels in the control group, only. Within the exercise-addicted group, withdrawal of exercise increased depressive mood symptoms, fatigue, confusion, anger, and a loss of vigor. Because of these results, Antunes and colleagues hypothesized that individuals with exercise addiction might have a dysfunctional eCB system.

Meanwhile, in a study of 49 obese men, which took part in a 1-year lifestyle modification program, including nutrition changes and physical activity, various anthropometric and metabolic risk factors, as well as the eCBs AEA and 2-AG before and after the 1-year lifestyle change, were measured. Unfortunately, the intensity and modality of the physical activity were not described further. However, AEA and 2-AG decreased significantly after a 1-year lifestyle change, while 2-AG correlated with decreased visceral adipose tissue and triacylglycerol levels (Di Marzo and others 2009).

Moreover, in a secondary analysis changes in mood after a 12 weeks program (anxiety, anger, TMD) as well as body weight were at least partly attributed to a significant decrease in AEA, which was measured at the beginning and end of the study (Oliveira and others 2019a). For this study, 30 healthy inactive men were divided into two groups. One group performed a 12-week sports program running three times a week for 40 minutes at the ventilatory threshold. The control group remained in their physically inactive lifestyle, defined as ≤1 day/week of leisure-time physical activity.

Discussion

This systematic review demonstrates that most studies published up to date reported a significant increase in eCBs after acute exercise. Those studies that did not find a significant increase in AEA used a low exercise intensity (Raichlen and others 2013) or a high latency until blood was sampled after the exercise task (Stensson and Grimby-Ekman 2019). Furthermore, habituation to exercise might play a role (Stone and others 2018). Meanwhile, an increase in 2-AG was only found in six out of 14 studies. One possible explanation could be the fact that several studies had small sample sizes, ranging from 8 to 21 exercising participants, suggesting they may have been insufficiently powered to detect changes in 2-AG. While acute exercise increases eCBs and eCB-like lipids, the contrary was found for long-term endurance exercise programs, which consistently found a decrease in eCB levels. However, the finding that long-term exercise programs decrease eCBs must be interpreted with caution. Up to date, only four studies were published on that topic and several possible biases must be considered. Apart from a possible reporting bias, changes in BMI and fat tissue following long-term exercise may have an impact on the eCB system.

One aim of this review was to summarize the current evidence regarding an association between the runner's high and the eCB system. From the core features of a runner's high (euphoria, anxiolysis, hypoalgesia, and sedation), sedation was the only one not assessed in human studies.

Exercise consistently had a positive effect on mood. For example, euphoria and feelings of happiness were reported after acute exercise (Siebers and others 2021). Another study found a significant association between positive affect and AEA levels after acute exercise, even though no significant increase in AEA through the exercise intervention was detected (Raichlen and others 2012). While the self-reported positive effects of endurance exercise are a robust finding across studies (Berger and Motl 2000; Reed and Ones 2006; Yeung 1996), the possible role of eCBs, and particularly AEA, has come into focus only recently.

The anxiolytic effect of exercise is well documented (Ensari and others 2015; Petruzzello and others 1991). In this review, 80% of the articles found an anxiolytic effect after a bout of exercise (see Table 1). Studies that investigated endurance exercise in vulnerable groups also detected significant effects on anxiety, for example, for people with major depression (Meyer and others 2019), migraine (Oliveira and others 2019b), substance use disorder (Brellenthin and others 2019), and posttraumatic stress disorder (Crombie and others 2018; Crombie and others 2019; Crombie and others 2020). The anxiolytic effects of a bout of exercise were also detected in an anxiety-provoking virtual reality paradigm (Siebers and others 2021). Moreover, associations with the eCB system were found in several studies. In exercising women suffering from major depression, a negative correlation between AEA levels and state anxiety (STAI) after exercise was found. In a study where participants received predictable and unpredictable electric shocks in an NPU task a higher increase in eCBs was associated with a higher decrease in anxiety and fear ratings (Crombie and others 2020).

Whether or not or under which circumstances exercise leads to hypoalgesia is still a matter of debate. From the studies reviewed here, one could find a hypoalgesic effect through pain measurement after 30 minutes of running (Crombie and others 2018), while in a group of patients with fibromyalgia and a control group no such effect was

detected (Stensson and Grimby-Ekman 2019). These inhomogeneous findings are also reflected in two reviews on this topic (Dannecker and Koltyn 2014; Koltyn 2000). Various variables seem to impact the detection of hypoalgesia after endurance exercise, namely, the method of pain testing, time-points of detection, instruments used for assessing pain (questionnaire, VAS), participants' health condition, exercise form, exercise intensity, and exercise duration.

A milestone in describing exercise-induced hypoalgesia in relation to the eCB system was the study of Koltyn and others (2014). This study was not included in this review because they used short-duration isometric exercise to study eCBs. They detected less pain after 3 minutes of submaximal isometric handgrip exercise. Furthermore, opioid blockade by naloxone did not demonstrate changes in pain perception. AEA, 2-AG, OEA, PEA, 2-OG, and N-docsahexaenoylethanolamine increased significantly postexercise. The latter showed a significant association with exercise-induced hypoalgesia (Koltyn and others 2014).

Even though a sedative effect of running is often assumed, none of the 21 studies reviewed here reported an effect of exercise on alertness. Thus, there is still no evidence that the fourth criterion of a runner's high, namely, sedation, is indeed associated with the eCB system. Meanwhile, a study in mice suggests that sedation is an unspecific consequence of exercise that does not require eCB signaling (Fuss and others 2015).

Provoking a runner's high might be challenged by several factors. Lactate thresholds might differ between individuals, and it is not possible to determine the lactate threshold for all persons at 85% of AAMHR or 75% VO_{2max} (Meyer and others 1999). Moreover, a rise in lactate levels in the blood can affect metabolization in the brain which might influence eCB signaling (Basso and Suzuki 2017). Thus, different exercise intensities and individual cardiorespiratory fitness levels might impact responses of the endocannabinoid system. Future research into endocannabinoid-mediated mechanisms might address these variations by measuring individual lactate changes or cardiorespiratory fitness.

These factors, as well as heterogeneities in how blood sampling and processing were performed, could explain the negative findings in some studies that investigated eCB after acute exercise.

The Hemostasis Theory

Several studies described a decrease in eCBs as a long-term consequence of an exercise program (Di Marzo and others 2009; Koay and others 2020; Oliveira and others 2019a; Oliveira and others 2019b) and 60 minutes postexercise (Stensson and Grimby-Ekman 2019). This was found for 2-AG after the 80-day exercise intervention (Koay and others 2020), as well as for AEA after a 12-week exercise program (Oliveira and others 2019a; Oliveira and others 2019b). The decrease in eCBs as a long-term consequence was also detected in a study in mice where the level of AEA even correlated negatively with the daily running distance after long-term wheel running (Biedermann and others 2016).

One possible mechanism is an increase in FAAH (fatty acid amide hydrolase) activity in lymphocytes, which was found in physically active men compared to sedentary controls (Gasperi and others 2014). In an in vitro experiment, IL-6 led to activation of the FAAH promoter in human lymphocytes. Thus, FAAH activity is enhanced and might modulate eCB levels in the plasma of physically active people. The authors hypothesized that the interaction between IL-6 (interleukin-6) and FAAH might be an adaptation process to cope with increased eCB levels in individuals performing endurance sports regularly (Gasperi and others 2014). This interesting mechanism should be further investigated in humans performing endurance exercise.

ECBs and the Influence on Stress

In the past, various studies demonstrated an association between the hypothalamic-pituitary-adrenal axis and eCBs. For example, a stress task can increase AEA levels (Crombie and others 2019). Furthermore, an increase in cortisol after exercise correlated with AEA levels (Heyman and others 2012). A further striking approach was made by Strewe and colleagues analyzing eCB levels in cosmonauts during spaceflight (Strewe and others 2012). ECBs were significantly increased during a parabolic flight and life onboard the International Space Station (ISS) in cosmonauts without motion sickness. These cosmonauts were in low-stress conditions. Conversely, in cosmonauts with motion sickness as well as higher-rated stress levels, an eCB increase was absent, and a massive rise in cortisol was detected.

Following the concept of allostasis helps us interpret the results. McEwen and Gianaros (2010) described that the body processes a stressor by physiological alterations of the HPA axis, hormones, autonomic nervous system, or cytokines to realize short-term adaptation, that is, allostasis. These mechanisms can lead to long-term dysregulation, contributing to chronic maladaptation, so-called allostatic load. Endurance sports, especially in clinical trials, might be a stressor. Thus, the increase in cortisol in the study of Heyman and others (2012) and Crombie and others (2019) is not surprising. Interestingly, there was a correlation between eCBs and cortisol, as well as increased eCB levels leading to the hypothesis that eCBs modulate stress responses (Hillard 2018). The release of

eCBs following exercise may thus be an important factor in shaping how the stress inflicted by exercise is perceived, which may be crucial in the long-term motivation to perform endurance exercise.

Limitations

Three studies did not report any intensity measures during endurance sports (Di Marzo and others 2009; Feuerecker and others 2012; Koay and others 2020). However, the description of the endurance exercise regime (1-year lifestyle program, 80-day Army Recruit Course, and hiking in the Alps) indicated that the intensity was rather high and should thus meet our endurance exercise inclusion criteria.

Future Research

An ongoing and open question is where and how exercise-induced eCBs may affect the brain. Using an fMRI task, increased activity in the caudate nucleus and hippocampus was found in a previous study also investigating eCBs (Marin Bosch and others 2020). However, no correlation between AEA release and brain activity was detected. Furthermore, all studies included in this work focus on eCB ligands in blood. However, there might be significant changes in the eCB receptor expression and activity in the brain as were shown in animal studies (de Chiara and others 2010; Di Marzo and others 2009; Gomes da Silva and others 2010; Zhou and Shearman 2004). A study protocol with a positron emission tomography and an eCB-ligand would be an important step toward the understanding of the brain structures involved with the positive effects of exercise-induced eCBs in humans (Boecker and others 2008).

We proposed that FAAH activity in lymphocytes may be responsible for the downregulation of the eCB system after long-term exercise, for example, to protect the body from high eCB levels (Gasperi and others 2014). This mechanism needs to be further studied.

Furthermore, there is still a lack of research regarding exercise-induced hypoalgesia during acute exercise. While some evidence suggests that exercise-induced hypoalgesia may be explained through endocannabinoid release during short-duration isometric exercise (Koltyn and others 2014), studies included in this review that investigated acute endurance exercise were inconsistent (Crombie and others 2018; Stensson and Grimby-Ekman 2019). Future research should address this topic.

Even though some people perform endurance exercise over several hours, up until today, no study evaluated eCB levels after 60 minutes at 70% to 85% of the AAMHR. It might be that the eCB system is also affected when energy metabolization processes of the body change during longer exercise regimes. A trial with sampling blood during a marathon would be an elegant path to evaluate the eCB system over time.

Next, just one study in this review was performed outside the laboratory (Feuerecker and others 2012). Surroundings during exercise might impact the eCB system and might help produce a runner's high. Future research should focus on such contextual factors.

Conclusion and a Recipe to Stimulate Endocannabinoid Release under Laboratory Conditions

Acute aerobic exercise was found to activate the eCB system. There were significant increases in AEA and less frequently in 2-AG after both preferred and prescribed exercise. Exercise-induced increases in eCBs seem to be associated with features of a runner's high, namely, decreased levels of anxiety and increased euphoria. There is some evidence that eCBs are associated with decreased perception of pain after exercise. Meanwhile, evidence for associations between eCBs and sedation postexercise are scarce, yet. Chronic aerobic exercise, on the other hand, is associated with decreased levels of eCBs and the neurobiological consequences of the supposed downregulation of the eCB system are not clear yet (Fig. 5).

After reviewing the existing literature, we suggest the following recommendations on how to stimulate endocannabinoid release under laboratory conditions and thus produce a runner's high:

- Running seems to be the best way to increase eCB levels in the blood, followed by cycling (Sparling and others 2003).
- Intensities of 70% to 85% of AAMHR imply to be the best range to achieve an increase in AEA and less frequently in 2-AG (Heyman and others 2012; Marin Bosch and others 2020; Raichlen and others 2013; Siebers and others 2021).
- Duration should be at least 20 minutes to achieve anxiolytic (Petruzzello and others 1991), analgesic (Rice and others 2019), and positive mood effects (Berger and Motl 2000). The highest positive mood effects can be expected after 30 to 35 minutes (Reed and Ones 2006).
- Surroundings, like exercising in nature, might play a significant role (Feuerecker and others 2012).
- Prior experience in the chosen exercise performance might play an essential role (Stone and others 2018).
- The highest eCB levels can be sampled immediately after exercise. An eCB increase can be detected up to 15 minutes postexercise (Cedernaes and others 2016; Heyman and others 2012).

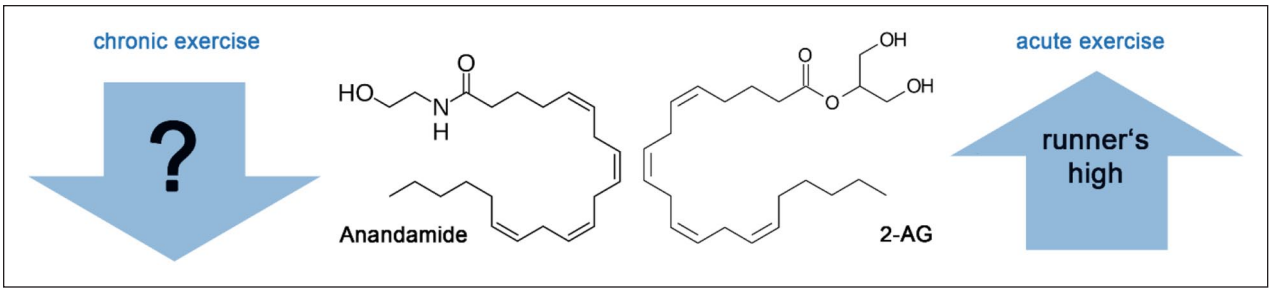

Figure 5. The endocannabinoids anandamide and 2-AG are increased after acute exercise and the increase is associated with features of the runner's high. In contrast, chronic exercise leads to a downregulation of the endocannabinoids and the neurobiological consequences of this downregulation are not yet clear.

- Positive affect can be detected at least 30 minutes postexercise (Reed and Ones 2006).
- Adequate questionnaires to analyze a runner's high are for euphoria a VAS, PANAS, or POMS, for anxiety the STAI, and for pain a standard numerical scale (Koltyn and others 2014).
- Methods for measuring individual fitness are the IPAQ (Siebers and others 2021) or, more invasive, lactate threshold measurement as well as $VO2_{max}$ measurement.

Author Contributions

MS and JF performed the searches and the screening of manuscripts. MS performed the data analysis. All authors assisted with data interpretation and drafting of the manuscript, as well as reading and approving the final version of the manuscript.

Declaration of Conflicting Interests

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Synopsis

Introduction

Some people experience an ephemeral feeling during endurance sports, called runner's high. This state's most prominent core features are elation (euphoria), reduced anxiety (anxiolysis), reduced pain sensitivity (hypoalgesia), and calming down (sedation) (Dietrich and McDaniel 2004). Furthermore, it is described as a feeling of effortlessness by a lost sense of time. The runner's high is most common during endurance running and less frequently detected during cycling (Sparling et al. 2003). The effect begins at least 20 min after endurance sports (Berger and Motl 2000; Petruzzello et al. 1991; Rice et al. 2019) and the highest impact of the core features can be detected 30 to 35 min after ending the exercise (Basso and Suzuki 2017) with an intensity of 70 to 85 % of the age-adjusted maximum heart rate (Raichlen et al. 2013). In addition, training exercise parameters like daytime, food intake, and surroundings may contribute to experiencing a runner's high (Feuerecker et al. 2012; Heyman et al. 2012).

In the 80s, the idea originated that endorphins produce the runner's high, based on inconsistent research results (Kraemer et al. 1989; Farrell et al. 1986; Carr et al. 1981). These molecules are hydrophilic and bind to the opioid system. Thus, they cannot pass the blood-brain barrier, limiting the evidence obtained from studies measuring endorphins in the periphery (Dietrich and McDaniel 2004). However, there is proof that endorphins influence brain functioning during endurance running (Boecker et al. 2008) and high-intensity training (Saanijoki et al. 2018). Today, especially in laymen, there is still the common belief that endorphins produce the runner's high.

On the other hand, there is the endocannabinoid (eCB) system which was identified in the 90s and consists, among other components, of two molecules: arachidonoyl ethanolamide (AEA) and 2-arachidonoyl glycerol (2-AG); two G-protein-coupled cannabinoid receptors CB1 and CB2; and a degrading enzyme: fatty acid amide hydrolase (FAAH). The eCB system is a unique endogenous system involved in different physiological processes distributed in the whole body (Howlett and Abood 2017). Prominent eCB functions are, for example, the regulation of energy metabolism, immunity, food intake, inflammation, gut-barrier function, neural development, memory processing, involvement in mood, and the feeling of anxiety. Furthermore, the molecules are lipophilic and can easily cross the blood-brain barrier so that some authors claimed that they are better candidates to mediate the runner's high (Dietrich and McDaniel 2004; Watkins 2018; Desai et al. 2021).

Based on the existing data, the first research question we wanted to answer was whether endorphins are mandatory to produce the runner's high in humans (Siebers et al. 2021). In the following study, we performed a systematic review to analyze the impact of our research

in the context of the current state of knowledge in the field. In addition, experimental strategies on how to produce elevated eCB levels under laboratory conditions were pointed out and recommendations for future research were given (Siebers et al. 2022).

Synopsis study one: Exercise-induced euphoria and anxiolysis do not depend on endogenous opioids in humans (Siebers et al. 2021)

The first study tried to corroborate the results of a previous study in mice in which anxiolysis and hypoalgesia effects after wheel running depended on eCB signaling (Fuss et al. 2015). In the study, it was possible to inhibit these effects by eCB receptor blockage, whereas an opioid receptor antagonist did not prevent an anxiolytic or hypoalgesic response. Furthermore, anxiolytic effects after exercise depended on CB1 receptors in the forebrain's GABAergic neurons. However, it is not yet possible to research one of the central core features of the runner's high in mice, namely euphoria.

To replicate these findings in humans, we focused on two aspects of the runner's high, euphoria and anxiolysis. The experimental design was as follows: 63 recreational running participants (32 female and 31 male) received the opioid receptor blocker naltrexone or an identical-looking placebo. The participants visited the laboratory twice to run or to walk for 45 min on a treadmill. The intensity was 70 to 85 % of the age-adjusted maximum heart rate (AAMHR) during running or under 50 % of the AAMHR during walking and was measured by a heart rate monitor watch. The emotional state was monitored by a visual analog scale and blood samples were taken to measure eCB levels before and after both exercise regimes. Next, an elevated plus-maze in a virtual reality scenario was used to investigate anxiolytic effects after both conditions. In the end, individuals were asked whether they had ever experienced a runner's high before in their life or during the visit.

The results indicated that opioid receptor blockage did not prevent exercise-induced euphoria or anxiolysis. On the contrary, running increased all measured eCBs and eCB-like molecules. Interestingly, the control condition walking also led to a significant increase, but two-fold lower than running. In comparison, running induced significantly more euphoria and reduced anxiety levels compared to walking. In both groups, identical numbers of participants reported a runner's high during the treadmill running and 69 % had previously experienced a runner's high. Surprisingly, one participant also described a runner's high during walking with an identical increase of eCBs as participants during the running condition.

In conclusion, the study indicates that the runner's high does not depend on opioid signaling and further suggests that the eCB system might be responsible for the runner's high as previously shown in mice. Unfortunately, it was impossible to inhibit the eCB system as the only CB1 and CB2 blocker rimonabant was withdrawn from the market (Sam et al. 2011).

However, using the opioid blocker naltrexone and sampling eCB levels in the blood plasma, provided a valid experimental approach to test the opposing endorphin and eCB hypotheses.

Synopsis study two: Do Endocannabinoids Cause the Runner's High? Evidence and Open Questions (Siebers et al. 2022)

After completion of the first study, the main goal was to integrate the results into the current state of knowledge in the field. In order to do this, a systematic research in PubMed/NCBI, Ovid MEDLINE, and Cochrane library was conducted with the Medical Subject Headings (MeSH) terms "Exercise" and "Endocannabinoids". The inclusion criteria established to identify suitable publications called for studies involving various endurance exercises which last at least 20 min with a low- to high-intensity level. In addition, inclusion also required that eCB levels were determined in blood before and after exercise or compared between groups. In total, from 278 records, 21 studies met the inclusion criteria and were included in the systematic review with a total number of 571 participants. The records were divided into acute aerobic exercise (17 studies; 378 participants) and chronic aerobic exercise (4 studies; 193 participants). Fourteen of 17 studies detected an increase in eCB levels after acute exercise. In contrast, all four studies regarding chronic exercise observed a decrease in eCB levels. More studies (14 of 17; 82 %) found an increase of AEA compared to 2-AG (five of 14; 52 %). Furthermore, nine of 11 studies (82 %) detected a positive effect on mood after acute exercise and eight of 10 studies (80 %) observed anxiolysis after a bout of exercise and long-term physical activity. Only two studies examined hypoalgesia, with inhomogeneous results, and no study investigated sedation.

In the discussion part of the publication, a recipe for producing a runner's high under laboratory conditions was developed, which advised that runningis the best way to increase eCB levels with an intensity of 70 to 85 % of AAMHR and a duration of at least 20 min. Furthermore, blood should be sampled immediately post-exercise. The evaluation of the data also suggested that the surroundings, e.g., laboratory or nature, and prior experience in the selected exercise might play a crucial role.

Other aspects of the discussion considered two hypotheses on how the eCB system might participate in regulatory systems. In the hemostasis hypothesis, the decrease of eCB levels in chronic exercise was explained by an increase of FAAH activity in lymphocytes and it was suggested that this might be an adaptation process to cope with increased eCB levels in regularly exercising individuals (Siebers et al. 2022). In the second hypothesis, it was proposed that eCBs might be a kind of eustress hormone preventing distress (Siebers et al. 2022).

In conclusion, the study corroborates the findings from study one that the eCB system plays a crucial role in producing a runner's high. Acute exercise causes anxiolytic and positive mood effects which are connected to the eCB system. The decrease of eCB levels after chronic exercise conditions is a recent observation that needs further investigation.

Discussion

Both studies indicate that eCBs play a central role in producing a runner's high. The widespread opinion that endorphins produce the runner's high was disproved in the first study. In study two, the increased eCB levels during running from study one, were compared with other studies. It was shown that two of four features of the runner's high are connected to the eCB system, namely euphoria and reduced anxiety, suggesting that the eCB system is instrumental in producing a runner's high. Furthermore, several studies demonstrated the influence of eCB signaling on exercise-induced hypoalgesia (Koltyn et al. 2014; Fuss et al. 2015; Crombie et al. 2018). However, the fourth criterion, sedation, is ambiguous and might not depend on eCB pathways (Fuss et al. 2015).

When evaluating the data in the field, one should be aware of the orchestral nature of pathways involving active molecules. For example, various other hormones like serotonin and dopamine, in addition to neurochemicals like lactate, cortisol as well as catecholamines might be linked to mood changes during endurance sports (Basso and Suzuki 2017). There is experimental evidence that endorphins play a key role in long-distance endurance running after one hour (Boecker et al. 2008), high-intensity exercises above the lactate threshold (Saanijoki et al. 2018), and in high-load resistance exercise (Kraemer et al. 1993) with blood flow restriction (Hughes and Patterson 2020). The eCB system, on the contrary, might be involved among various pathways in sports physiology during endurance exercise, and the transmission to other connected systems might depend on exercise parameters such as intensity and duration (Ekkekakis et al. 2011).

The systematic review demonstrated a decrease in eCB levels associated with chronic exercise. The reduction is in line with a previous study in mice (Biedermann et al. 2016). One possible explanation for this finding might be that the body's regulatory system tries to avoid elevated eCB levels by downregulation of the eCB system. The downregulation might occur because of an enhanced FAAH activity in lymphocytes (Gasperi et al. 2014).

This hypothesis opens the door for further speculations. Endurance sports can be addictive (Antunes et al. 2016) and the eCB system is involved in reward processes (Spanagel 2020). Thus, to obtain activation of the reward circuit, it might be necessary to run longer or with a higher intensity to achieve a runner's high after chronic exercise.

One study addressing acute exercise with blood sampling after 15 min post-exercise demonstrated no increase of AEA (Cedernaes et al. 2016) and one study even described a

decrease of eCB levels 60 min post-exercise (Stensson and Grimby-Ekman 2019). Therefore, we advise to sample blood immediately post-exercise. Taking together, one might recommend athletes not to take a pause or slow down but to keep on running during a bout of exercise. Otherwise, the eCB levels might decrease and not provide benefits. That being said, the decrease of eCB levels might also contribute to a well-known and feared syndrome in endurance running: hitting the wall (Venhorst et al. 2018; Smyth 2021). The syndrome appears approximately at kilometer 30 and is described by physical and psychological exhaustion, resulting in a loss of performance. Among the depletion of the energy stores and possible hypoglycemia, the decrease of eCB levels after a pause might contribute to hitting the wall phenomena.

Due to methodological hurdles, there is no complete proof that the eCB system is responsible for the runner's high and it will be the work of future research to overcome those obstacles. For example, a study protocol of Boecker et al. (Boecker et al. 2008) using positron emission tomography and a radioligand binding to the eCB receptors after running might give us further information about eCB signaling in the brain.

In line, no study sampled eCB levels after one hour of endurance sports, e.g., during a marathon. It might be that with changing energy metabolization endocrinological pathways change.

Last but not least, one participant in the first study described a runner's high during walking with elevated eCB levels comparable to participants during running. Furthermore, walking also led to a significant increase of eCB levels in study one. There is proof that conditions other than running activate the eCB system. For example, hiking (Feuerecker et al. 2012), masturbation (Fuss et al. 2017), Yoga (Sadhasivam et al. 2020), and singing (Stone et al. 2018) increase eCB levels. Additionally, in a study of cosmonauts during a parabolic space flight, eCB levels were significantly increased in individuals without motion sickness (Strewe et al. 2012). Accordingly, some authors propose that eCBs are a sort of eustress hormone preventing distress (Strewe et al. 2012; Siebers et al. 2022).

Interestingly, some clinical studies have focused on activating the eCB system with endurance sports as a medical treatment in vulnerable groups. For instance, in individuals with posttraumatic stress disorder (Crombie et al. 2018b; Crombie et al. 2019; Crombie et al. 2020), major depression (Meyer et al. 2019), migraine (Oliveira et al. 2019), and substance use disorder (Brellenthin et al. 2019), endurance sports were seen as a possible adjuvant treatment. How and in which way the eCB system is a possible treatment in vulnerable groups is still the subject of debate. However, the observed anxiolytic and euphoric effects of endurance exercise might help to improve the well-being of vulnerable groups.

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Abstract

A runner's high describes a sense of well-being during endurance exercise characterized by euphoria, anxiolysis, hypoalgesia and sedation. It has been a widespread belief that the release of endorphins underlies a runner's high. However, exercise releases two classes of rewarding molecules, endocannabinoids (eCBs) and endorphins. Study one investigated whether the development of euphoria and anxiolysis depend on opioid signaling by using the opioid receptor antagonist naltrexone in a double-blind, randomized, placebo-controlled experiment. Participants (N = 63) exhibited increased euphoria and decreased anxiety after 45 min of running on a treadmill compared to walking and running led to higher plasma eCB levels. Opioid blockage did not prevent the development of euphoria and reduced anxiety. Therefore, this study provides evidence that a runner's high does not depend on endorphins. In study two, the results were integrated into the existing scientific knowledge on this subject. All data from clinical trials in humans on eCB levels following exercise until April 20, 2021 were sampled. From 278 records, 21 met the inclusion criteria. After acute exercise, 14 of 17 studies detected an increase in eCBs. In contrast, after a period of long-term endurance exercise, four articles described a decrease in eCBs. In conclusion, acute aerobic exercise was found to activate the eCB system accompanied by anxiolysis and euphoria, making eCBs strong candidates for producing the runner's high.

Zusammenfassung

Ein Läuferhoch beschreibt einen euphorischen Zustand während dem Ausdauersport begleitet von Anxiolyse, Hypoalgesie und Sedation. Lange Zeit wurde angenommen, dass Endorphine für das Läuferhoch verantwortlich sind. Jedoch werden während des Ausdauersports zwei Sorten von Belohnungs-Molekülen ausgeschüttet: Endocannabinoide (eCB) und Endorphine. In der ersten Studie wurde untersucht in welchem Maße Endorphine verantwortlich sind, indem in einer Placebo-kontrollierten, doppelblinden, randomisierten Studie die Hälfte der 63 Läufer*innen den Opioid Blocker Naltrexon erhielten. Die Läufer*innen zeigten erhöhte Euphorie und reduzierte Angst nach einem 45 min Dauerlauf im Vergleich zu Gehen auf dem Laufband. Joggen erhöhte die eCB Plasmawerte und Opioid Blockade konnte weder Euphorie noch Anxiolyse verhindern. Somit zeigt die Studie, dass die Entwicklung eines Läuferhochs unabhängig von Endorphinen passiert. In der zweiten Studie wurden die Ergebnisse in den aktuellen Wissensstand eingeordnet. Dafür wurden alle klinischen Studien bezüglich Ausdauersport und eCB in Menschen bis zum 20. April 2021 eingeschlossen. Von 278 Arbeiten erfüllten 21 Studien die Einschlusskriterien. Vierzehn von 17 Studien beschrieben nach akutem Ausdauersport einen Anstieg von eCB, während vier Artikel nach einem längeren Trainingsprogram einen Abfall von eCB zeigten. Zusammenfassend wurde eine Aktivierung des eCB Systems begleitet von weniger Angst und Euphorie gefunden, was es sehr wahrscheinlich macht, dass eCB für das Läuferhoch verantwortlich sind.

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Author contributions study one

Michael Siebers, Sarah V. Biedermann and Johannes Fuss designed the study, analyzed the data, and wrote the first draft of the manuscript. Michael Siebers collected data. Laura Bindila and Beat Lutz performed the endocannabinoid measurement and contributed to the preparation of the manuscript. All authors commented on and approved the final manuscript.

Author contributions study two

Michael Siebers and Johannes Fuss performed the searches and the screening of manuscripts. Michael Siebers performed the data analysis. All authors assisted with data interpretation and drafting of the manuscript, as well as reading and approving the final version of the manuscript.

Author contribution synopsis

Michael Siebers wrote the synopsis.

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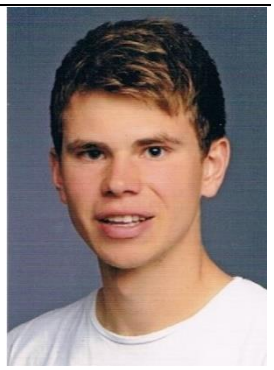

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■ PUBLICATIONS

Siebers, Michael; Biedermann, Sarah V.; Bindila, Laura; Lutz, Beat; Fuss, Johannes (2021): Exercise-induced euphoria and anxiolysis do not depend on endogenous opioids in humans. In *Psychoneuroendocrinology* 126, p. 105173. DOI: 10.1016/j.psyneuen.2021.105173.

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