Eur J Appl Physiol (2013) 113:869–875
DOI 10.1007/s00421-012-2495-5

ORIGINAL ARTICLE

Exercise-induced endocannabinoid signaling is modulated by intensity

David A. Raichlen · Adam D. Foster · Alexandre Seillier · Andrea Giuffrida · Gregory L. Gerdeman

Received: 22 May 2012 / Accepted: 6 September 2012 / Published online: 19 September 2012

Abstract Endocannabinoids (eCB) are endogenous ligands for cannabinoid receptors that are densely expressed in brain networks responsible for reward. Recent work shows that exercise activates the eCB system in humans and other mammals, suggesting eCBs are partly responsible for the reported improvements in mood and affect following aerobic exercise in humans. However, exercise-induced psychological changes reported by runners are known to be dependent on exercise intensity, suggesting that any underlying molecular mechanism should also change with varying levels of exercise intensity. Here, we examine circulating levels of eCBs following aerobic exercise (treadmill running) in recreationally fit human runners at four different intensities. We show that eCB signaling is indeed intensity dependent, with significant changes in circulating eCBs observed following moderate intensities only (very high and very low intensity exercises do not significantly alter circulating eCB levels). Our results are consistent with intensity-dependent psychological state changes with exercise and therefore support the hypothesis that eCB activity is related to neurobiological effects of exercise. Thus, future studies examining the role of exercise-induced eCB signaling on neurobiology or physiology must take exercise intensity into account.

Keywords AEA · 2-AG · Positive affect · Endurance running · Neurogenesis · Analgesia

Communicated by Fausto Baldissera.

D. A. Raichlen (✉) · A. D. Foster
School of Anthropology, University of Arizona, Tucson, AZ 85721, USA
e-mail: raichlen@email.arizona.edu

A. Seillier · A. Giuffrida
Department of Pharmacology, University of Texas Health Science Center, San Antonio, TX, USA

G. L. Gerdeman
Department of Biology, Eckerd College, St. Petersburg, FL, USA

Introduction

Humans frequently report a neurobiological response to exercise that includes both central effects (improved affect, sense of well-being, anxiety reduction, post-exercise calm) and peripheral effects (reduced pain sensation) (Dietrich and McDaniel 2004; Ogles and Masters 2003; Sachs and Pargman 1979). Recent work in humans and animal models suggests that endocannabinoid (eCB) signaling plays an important role in generating these exercise-induced responses (Dubreucq et al. 2010; Hill et al. 2010; Keeney et al. 2008, 2012; Raichlen et al. 2012; Rasmussen and Hillman 2011; Sparling et al. 2003). ECBs are endogenous ligands for the CB_1 and CB_2 cannabinoid receptors, which were originally identified as the receptors activated by Δ^9-tetrahydrocannabinol (THC; the principal psychoactive ingredient in marijuana) (Piomelli 2003). CB_1 receptors are found in numerous brain areas, but are particularly dense in regions associated with emotion, cognition, motor behavior, and reward (Glass et al. 1997). The two most studied eCBs, anandamide (AEA) and 2-arachidonylglycerol (2-AG), are released by neurons in an activity-dependent manner to modulate synaptic activity and plasticity (Gerdeman 2008; Katona and Freund 2008; Piomelli 2003). Through this activity, eCBs may contribute to exercise-related changes in psychological state that are popularly referred to as the 'runner's high' (Dietrich and McDaniel 2004).

Several lines of evidence suggest that the eCB system is involved in neurobiological rewards associated with aerobic exercise and may function to motivate endurance exercise and reduce pain sensitivity (Dietrich and McDaniel 2004; Keeney et al. 2008, 2012; Raichlen et al. 2012; Sparling et al. 2003). First, circulating levels of eCBs increase following treadmill running and cycling in humans (Raichlen et al. 2012; Sparling et al. 2003). Since eCBs are highly lipophilic, circulating eCBs can readily pass through the blood–brain barrier, leading to central effects (Dietrich and McDaniel 2004). Note that movement of eCBs across biological membranes is facilitated by recently characterized transporter proteins (Fu et al. 2012) and might be dynamically modified by physiological processes. Second, studies of animal models suggest a role for eCBs in the motivation to exercise (Dubreucq et al. 2010; Keeney et al. 2008, 2012; Rasmussen and Hillman 2011). Although we must be careful in applying results from animal studies directly to humans, these experimental designs allow researchers to explore mechanisms at a more detailed level than is possible in human studies. For example, in cannabinoid (CB) receptor knockout mice, voluntary wheel-running is significantly reduced compared with control groups (Dubreucq et al. 2010). This reduction suggests that the eCB system is involved in the motivation for voluntary exercise in these animal models. Additionally, in female mice that have undergone artificial selection for high amounts of voluntary wheel-running, administration of rimonabant (SR141716; a CB_1 receptor antagonist) or WIN 55,212-2 (a CB_1 receptor agonist) significantly reduced wheel-running compared with mice that have not undergone the selection experiment (Keeney et al. 2008, 2012). The fact that selected mice experience a differential response to eCB signaling suggests that evolution can act on the eCB system to help motivate exercise (Keeney et al. 2008, 2012). Finally, Rasmussen and Hillman (2011) reported the complementary finding that in Long-Evans rats, rimonabant injections suppressed operant responding to attain access to a running wheel, again supporting a role for eCB signaling in the reinforcing properties of exercise.

Exercise-induced eCB activity in humans appears to be altered by exercise intensity (Feuerecker et al. 2012; Heyman et al. 2012; Raichlen et al. 2012), which is consistent with findings that the neurobiological effects of exercise are also intensity dependent (Berger and Motl 2000; Reed and Ones 2006). In general, neurobiological effects of exercise follow a 'u-shaped' curve, with the greatest effects occurring at medium levels of intensity and minimal effects occurring at low and high intensity levels (Berger and Motl 2000; Reed and Ones 2006). Raichlen et al. (2012) showed that, in humans and dogs, AEA levels increase at moderate (70 % of maximum heart rate in humans) rather than at low (45 % of max. heart rate) exercise intensities. Heyman et al. (2012) found that circulating AEA (but not 2-AG) levels increase following exercise at both 55 and 75 % of maximal power output during cycling, and the increase, relative to baseline, is greatest following the highest exercise intensity. However, in this study, subjects performed both exercise intensities in the same testing session, making it difficult to determine whether increased eCB activity was due to intensity alone, or whether it was affected by exercise duration. Feuerecker et al. (2012) measured changes in AEA following physical activity outside of the laboratory in more natural settings. Subjects completed three exercise protocols. On different days, subjects hiked at low altitude, hiked to a high-altitude location, or took a helicopter to high altitude for similar durations ($\sim$3–5 h). Circulating AEA increased under both hiking conditions, but more so on the strenuous hike to altitude, and did not increase in the passive travel condition (helicopter to high altitude), which suggests strenuous exercise leads to a greater increase in AEA. While these studies are informative, their methods do not readily show how circulating AEA levels respond under more standardized exercise conditions (i.e., exercise at specific intensities).

The purpose of this study is to examine changes in circulating eCBs following exercise at a wide variety of intensities under standardized conditions. Here, we examine circulating eCBs before and after exercise at four different intensities, with each measurement occurring on a separate day. We predicted that peripheral levels of eCBs would increase following moderate- or high-intensity exercise, but not following low-intensity exercise.

Methods

Participants

Ten healthy subjects participated in this study. The subject group included six males and four females who are all self-reported fit, healthy, regular runners (see Table 1). All subjects were instructed not to exercise outside of the laboratory on data collection days and fasted for 3 h prior to coming to the lab. All procedures were approved by the University of Arizona Institutional Review Board, and subjects gave their informed consent prior to the beginning of the study.

Procedures

Subjects came to the laboratory on five separate occasions at the same time of day for each visit. The first day was a general information session to let them become familiar with the procedures and requirements of the study. On

Table 1 Subject characteristics

Variable	Mean	Standard deviation
Body mass (kg)	67.35	9.06
Age (years)	31.91	12.08
Heart rate at intensity I (%)	44.6	4.16
Heart rate at intensity II (%)	72.48	8.43
Heart rate at intensity III (%)	83.23	7.48
Heart rate at intensity IV (%)	92.1	6.47

Heart rates are reported here as a percent of age-adjusted maximum heart rate (see text for further explanation)

exercise testing days, blood samples were taken prior to treadmill running (see *Blood sample procedures* below). Subjects were then asked to walk or run on the treadmill at one of four intensities for 30 min (see Table 1). A second blood sample was taken immediately following each exercise trial. The order of intensities was randomized for each participant. Each participant exercised at a single intensity on a given day.

Exercise intensity

Age-adjusted maximum heart rate (AAMHR) was used to measure exercise intensity and was calculated following Tanaka et al. (2001). During each treadmill trial, subjects wore heart rate monitors (Polar RS400 heart rate monitor) for determination of exercise intensity. Treadmill speeds were adjusted to elicit heart rates as percentages of AAMHR at four different intensities (see Table 1). The lowest corresponded to a moderate walking speed (intensity I–HR <50 % AAMHR). The other three intensities were a slow jog (intensity II–HR ~70 % AAMHR), a medium-intensity run (intensity III–HR ~80 % AAMHR), and a high-intensity run (intensity IV–HR ~90 % AAMHR).

Blood sample procedures

Blood samples (0.5 ml) were collected before and after each of these trials using a syringe filled with 1 ml of Krebs-Tris buffer/EDTA (4.5 mM). Samples were immediately centrifuged in Accuspin tubes (Sigma) at $800\times g$, for 10 min. Methods for eCB extraction and quantification by GC/MS isotope dilution are described in detail in Hardison et al. (2006).

Data analysis

Because day-to-day fluctuations in baseline eCB levels are known to occur in healthy individuals (Vaughn et al. 2010; Zoerner et al. 2009), we investigated the change in circulating eCBs from pre- to post-exercise values on a given day only. We used a two-way repeated-measures ANOVA [time of blood sample (pre- vs. post-exercise) × intensity] to compare pre- and post-exercise eCB levels across the four speeds. If a significant interaction between the two independent variables was found, we examined which intensities elicited a significant post-exercise change in eCB level using Fisher's least significant differences (LSD) post hoc test to control for multiple comparisons. If the time × intensity interaction was significant, we examined the effect of intensity on the magnitude of the change in eCB levels using a one-way repeated-measures ANOVA where the dependent variable was the difference between pre- and post-exercise eCB and the independent variable was intensity level. Finally, we used a Fisher's LSD post hoc test to determine which intensities significantly differed.

Results

Heart rates as a percentage of AAMHR differed significantly across the four exercise intensities (one-way repeated-measures ANOVA: $F[3, 27] = 194.41$, $p < 0.001$). A Fisher's LSD post hoc analysis found that heart rate as a percentage of AAMHR increased significantly at increasing intensity levels (Table 2). A two-way repeated-measures ANOVA (time of blood sample [pre- vs. post-exercise] × intensity) found a significant effect of time ($F[1, 9] = 7.36$, $p = 0.02$), intensity ($F[3, 27] = 4.60$, $p = 0.01$), and the interaction between time and intensity ($F[3, 27] = 3.42$, $p = 0.03$) on AEA levels (Fig. 1). However, a two-way repeated-measures ANOVA (time of blood sample × intensity) of 2-AG found no significant effect of time ($F[1, 9] = 0.018$, $p = 0.90$), intensity ($F[3, 27] = 0.964$, $p = 0.42$), or the interaction between time and intensity ($F[3, 27] = 0.965$, $p = 0.42$). Therefore, we investigated changes in AEA only, using a post hoc analysis. A Fisher's LSD post hoc test showed that exercise intensities II and III led to a significant increase in post-exercise AEA levels (Fig. 1). A one-way repeated-measures ANOVA found that exercise intensity had a significant effect on the magnitude of the difference between post- and pre-exercise values of AEA ($F[3, 27] = 3.42$, $p = 0.03$), and a Fisher's LSD found that exercise

Table 2 Fisher's LSD post hoc test statistics for difference in heart rate as a percentage of maximum heart rate across intensities

Intensity	II	III	IV
I	**13.42 (<0.00001)**	**18.59 (<0.00001)**	**22.86 (<0.00001)**
II	x	**5.17 (0.00006)**	**5.17 (0.00006)**
III		x	**4.27 (0.0005)**

Values given are *t*-statistic (*p* values) for pair-wise comparisons. Bold values are significant at alpha = 0.05

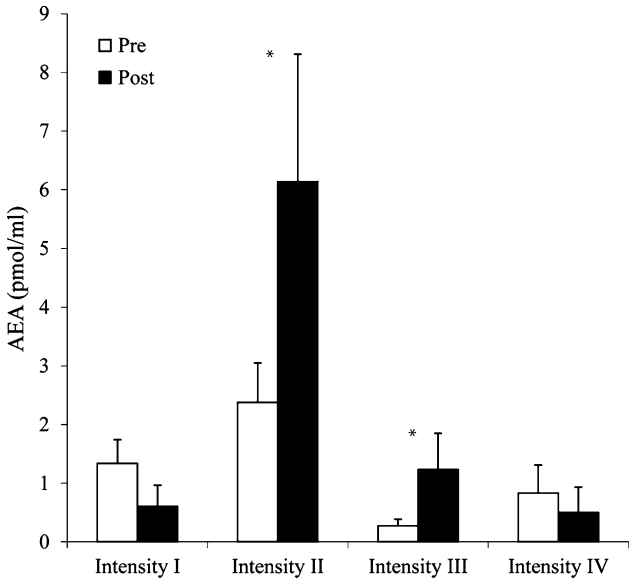

Fig. 1 Change in AEA levels following exercise at different intensities. *Stars* represent significant differences (pre vs. post at each intensity) following Fisher's LSD post hoc tests ($p < 0.05$)

Table 3 Fisher's LSD post hoc test statistics for difference in post- and pre-exercise levels of AEA

	II	III	IV
I	**2.86 (0.005)**	1.34 (0.097)	0.22 (0.412)
II	x	−1.52 (0.070)	**−2.63 (0.008)**
III		x	−1.12 (0.140)

Values given are *t*-statistic (*p* values) for pair-wise comparisons. Bold values are significant at alpha = 0.05

intensity II had a significantly greater difference between post- and pre-exercise levels of AEA compared with intensities I and IV (Table 3).

Discussion

Our data show that exercise-induced AEA release in the bloodstream is dependent on exercise intensity. Only moderate exercise intensities (~70–85 % of AAMHR) lead to significant changes in circulating levels of AEA. Circulating levels of 2-AG are not influenced by exercise at any intensity. We build on the results of Sparling et al. (2003) who showed an increase in AEA, but not 2-AG, at a moderate intensity of exercise. In addition, our results support and help clarify recent work showing that higher intensities elicit higher levels of circulating AEA (Feuerecker et al. 2012; Heyman et al. 2012). Here, we show that there is a relatively narrow window of exercise intensities that elicit an eCB response and that intensities corresponding to walking speeds do not generate an increase in circulating eCBs.

These results are particularly important given the possible functions of the eCB system during exercise. Dietrich and McDaniel (2004) proposed a role for the endocannabinoid system in the neurobiological rewards associated with exercise. As described above, this hypothesis is supported by a range of both human and nonhuman mammalian studies (Dietrich and McDaniel 2004; Keeney et al. 2008, 2012; Raichlen et al. 2012; Sparling et al. 2003). Our results confirm previous work showing that these rewards follow a U-shaped curve with respect to exercise intensity (e.g., Berger and Motl 2000). For example, the change in psychological state associated with running in humans is generally only present at moderate intensities, whereas low and high intensities lead to limited changes in mood or affective state (Berger and Motl 2000; Kirkcaldy and Shephard 1990).

In addition to neurobiological rewards, eCB signaling may have important peripheral effects that likely aid exercise performance. Specifically, Sparling et al. (2003) suggested that eCB signaling during exercise may reduce pain sensitivity associated with intense physical activity. There is a growing body of evidence suggesting that eCBs effectively mitigate chronic and acute pain at both central and peripheral sites (Agarwal et al. 2007; Gerdeman 2008; Hohmann and Suplita 2006; Hohmann et al. 1999, 2005; Ibrahim et al. 2003; Piomelli 2003; Richardson 2000; Meng et al. 1998) and therefore likely play a role in exercise-induced analgesia. Peripheral analgesia by eCBs is achieved through CB_1-mediated inhibition of neurotransmitter release in nociceptive afferent pathways of the peripheral nervous system (Agarwal et al. 2007; Gerdeman 2008; Piomelli 2003) and via activation of CB_2 receptors, which inhibit the release of inflammatory mediators (Hohmann and Suplita 2006; Ibrahim et al. 2003). A great deal of work has shown that exercise has analgesic effects (Koltyn 2002), which likely contribute to feelings of effortlessness associated with the neurobiological rewards during exercise (i.e., 'runner's high'), and may improve athletic performance by allowing athletes to exercise at higher intensities for longer periods of time (Dietrich and McDaniel 2004). Our results are consistent with studies showing intensity-dependent effects of exercise on pain sensitivity, with low intensities generally reducing the level of analgesia experienced by athletes (Hoffman et al. 2004; Koltyn 2002).

Finally, recent work in animal models implicates eCB signaling in exercise-induced adult hippocampal neurogenesis (Hill et al. 2010; Wolf et al. 2010), which may improve memory and increase the volume of brain structures in young and elderly human populations (Erickson et al. 2011). Neural progenitor cells express CB receptors,

and experimental studies show that they synthesize eCBs (Hillard 2000; Howlett et al. 2004). The presence of AEA is essential for neurogenesis (Aguado et al. 2005, 2006), and genetic deletion of FAAH (fatty acid amide hydrolase), the enzyme responsible for AEA hydrolysis, significantly increases cell proliferation in the dentate gyrus (Aguado et al. 2005, 2006). It should be noted that one study (Dubreucq et al. 2010) found that CB_1 knockout mice had similar levels of activity-induced neurogenesis compared with wild-type littermates. Thus, the role of eCB signaling in adult exercise-induced neurogenesis requires more experimental work. An additional caveat of these studies is that neurogenesis cannot be directly measured in humans, so we must interpret results from animal models with caution. Despite these caveats, our results are consistent with limited evidence for an intensity-dependent relationship between exercise and neurogenesis. Two studies show that hippocampal neurogenesis is reduced when rodents are forced to run at very high intensities on treadmills, whereas it is significantly increased at lower and moderate intensities (Kim et al. 2003; Lou et al. 2008).

In addition to possible functional effects of eCB signaling, we can view our results through the evolutionary lens suggested by Raichlen et al. (2012). In taxa that evolved to run long distances, AEA levels increase following moderate-, but not low-intensity exercise (Raichlen et al. 2012). However, exercise-induced eCB activity did not occur in taxa that do not generally use high-intensity aerobic activity in their foraging behaviors (Raichlen et al. 2012). Thus, mechanisms to enhance eCB signaling during exercise may have evolved in the distance-running taxa to motivate and reward running as an essential foraging behavior, and would provide the additional benefit of mitigating pain and inflammation incurred during running. Our results suggest that any evolutionary link between AEA and exercise in humans is restricted to moderate, rather than very high or very low exercise intensities. These results are consistent with anatomical and physiological evidence that humans evolved as aerobic athletes, and that moderate, rather than very high or very low, intensities were important for foraging success during human evolution (Bramble and Lieberman 2004; Carrier 1984; Lieberman et al. 2006, 2007, 2009).

Although our results are consistent with these neurobiological and physiological functions associated with eCB signaling, it is important to note that this study measured peripheral eCB signaling only, and thus, we cannot be sure that our measurements fully reflect changes in eCBs within the central nervous system. However, previous work strongly suggests that peripheral levels of eCBs are reflective of central levels, given their ability to readily traverse the blood–brain barrier (Dietrich and McDaniel 2004; Glaser et al. 2006; Willoughby et al. 1997). For example, peripheral intravenous injection of AEA in rodents leads to increased AEA and dopamine levels in brain reward regions (Solinas et al. 2006; Willoughby et al. 1997). Additionally, intravenous injections of eCBs activate CB receptors in the brain and lead to reward-seeking behaviors (e.g., self-administered injections) in animal models (Justinova et al. 2005, 2011; Solinas et al. 2006; Willoughby et al. 1997).

In conclusion, exercise activates the eCB system in a narrow window of exercise intensities. Our results suggest that studies specifically testing for the neurobiological effects of eCB signaling must take into account exercise intensity since exercise at either very high or very low intensities may not elicit eCB activity. Through these kinds of studies, we can more effectively prescribe exercise in ways that benefit psychological state, pain management, and overall cognitive health.

Acknowledgement The staff of the Clinical and Translational Science Research Center at the University of Arizona assisted with data collection. This project was supported by NSF BCS 0820270 and a Wenner Gren Foundation Hunt Post-Doctoral Fellowship to D.A.R.

References

Agarwal N, Pacher P, Tegeder I, Amaya F, Constantin CE, Brenner GJ, Rubino T, Michalski CW, Marsicano G, Monory K, Mackie K, Marian C, Batkai S, Parolaro D, Fischer MJ, Reeh P, Kunos G, Kress M, Lutz B, Woolf CJ, Kuner R (2007) Cannabinoids mediate analgesia largely via peripheral type 1 cannabinoid receptors in nociceptors. Nat Neurosci 10:870–879

Aguado T, Monory K, Palzuelos J, Stella N, Cravatt B, Lutz B, Marsicano G, Kokaia Z, Guzman M, Galve-Roperh I (2005) The endocannabinoid system drives neural progenitor proliferation. FASEB Journal 19:1704–1706

Aguado T, Palzuelos J, Monory K, Stella N, Cravatt B, Lutz B, Marsicano G, Kokaia Z, Guzman M, Galve-Roperh I (2006) The endocannabinoid system promotes astroglial differentiation by acting on neural progenitor cells. J Neurosci 26:1551–1561

Berger BG, Motl RW (2000) Exercise and mood: a selective review and synthesis of research employing the profile of mood states. J Appl Psychol 12:69–92

Bramble DM, Lieberman DE (2004) Endurance running and the evolution of *Homo*. Nature 432:345–352

Carrier DR (1984) The energetic paradox of human running and hominid evolution. Curr Anthropol 25:483–495

Dietrich A, McDaniel WF (2004) Endocannabinoids and exercise. Br J Sports Med 38:536–541

Dubreucq S, Koehl M, Abrous DN, Marsicano G, Chaouloff F (2010) CB1 receptor deficiency decreases wheel-running activity: consequences on emotional behaviours and hippocampal neurogenesis. Exp Neurol 224:106–113

Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H, White SM, Wojcicki TR, Mailey E, Vieira VJ, Martin SA, PB D, Woods JA, McAuley E, Kramer AF (2011) Exercise training increases size of hippocampus and improves memory. Proc Nat Acad Sci USA 108:3017–3022

Feuerecker M, Hauer D, Toth R, Demetz F, Holzl J et al (2012) Effects of exercise stress on the endocannabinoid system in humans under field conditions. Eur J Appl Physiol 112: 2777–2781

Fu J, Bottegoni G, Sasso O, Bertorelli R, Rocchia W, Masetti M, Guijarro A, Lodola A, Armirotti A, Garau G, Banderiera T, Reggiani A, Mor M, Cavalli A, Piomelli D (2012) A catalytically silent FAAH-1 variant drives anandamide transport in neurons. Nat Neurosci 15:64–69

Gerdeman GL (2008) Endocannabinoids at the synapse - retrograde signaling and presynaptic plasiticity in the brain. In: Kofalvi A (ed) Cannabinoids and the Brain. Springer-Verlag, New York, pp 203–236

Glaser ST, Gatley SJ, Gifford AN (2006) Ex vivo imaging of fatty acid amide hydrolase activity and its inhibition in the mouse brain. J Pharmacol Exp Ther 316:1088–1097

Glass M, Dragunow M, Faull RLM (1997) Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. Neuroscience 10:1665–1669

Hardison A, Weintraub ST, Giuffrida A (2006) Quantification of endocannabinoids in rat biological samples by GC/MS: technical and theoretical considerations. Prostaglandins Other Lipid Mediat 81:106–112

Heyman E, Gamelin FX, Goekint M, Piscitelli F, Roelands B, Leclair E, Di Marzo V, Meeusen R (2012) Intense exercise increases circulating endocannabinoid and BDNF levels in humans: possible implications for reward and depression. Psychoneuroendocrinology 37:844–851

Hill MN, Titterness AK, Morrish AC, Carrier EJ, Lee TTY, Gil-Mohapel J, Gorzalka BB, Hillard CJ, Christie BR (2010) Endogenous cannabinoid signaling is required for voluntary exercise-induced enhancement of progenitor cell proliferation in the hippocampus. Hippocampus 20:513–523

Hillard CJ (2000) Biochemistry and pharmacology of the endocannabinoids arachidonylethanolamide and 2-arachidonylglycerol. Prostaglandins Other Lipid Mediat 61:3–18

Hoffman MD, Shepanski MA, Ruble SB, Valic Z, Buckwalter JB, Clifford PS (2004) Intensity and duration threshold for aerobic exercise-induced analgesia to pressure pain. Arch Phys Med Rehabil 85:1183–1187

Hohmann AG, Suplita RL (2006) Endocannabinoid mechanisms of pain modulation. AAPS J 8:E693–E708

Hohmann AG, Tsou K, Walker JM (1999) Cannabinoid suppression of noxious heat-evoked activity in wide dynamic range neurons in the lumbar dorsal horn of the rat. J Neurophysiol 81:575–583

Hohmann AG, Suplita RL, Bolton NM, Neely MH, Fegley D, Mangieri R, Krey JF, Walker JM, Holmes PV, Crystal JD, Duranti A, Tontini A, Mor M, Tarzia G, Piomelli D (2005) An endocannabinoid mechanism for stress-reduced analgesia. Nature 435:1108–1112

Howlett AC, Breivogel CS, Childer SR, Deadwyler SA, Hampson RE, Porrino LJ (2004) Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects. Journal of Clinical Investigation 115:3104–3116

Ibrahim MM, Deng H, Zvonok A, Cockayne DA, Kwan J, Mata HP, Vanderha TW, Lai J, Porreca F, Makriyannis A, Malan TP (2003) Activation of CB2 cannabinoid receptors by AM1241 inhibits experimental neuropathic pain: pain inhibition not present in CNS. Proc Nat Acad Sci USA 100:10529–10533

Justinova Z, Solinas M, Tanda G, Redhi GH, Goldberg SR (2005) The endogenous cannabinoid anandamide and its synthetic analog R(+)-methanandamide are intravenously self-administered by squirrel monkeys. J Neurosci 25:5645–5650

Justinova Z, Yasar S, Redhi GH, Goldberg SR (2011) The endogenous cannabinoid 2-arachidonoylglycerol is intravenously self-administered by squirrel monkeys. J Neurosci 31:7043–7048

Katona I, Freund TF (2008) Endocannabinoid signaling as a synaptic circuit breaker in neurological disease. Nat Med 14:923–930

Keeney BK, Raichlen DA, Meek TH, Wijeratne RS, Middleton KM, Gerdeman GL, Garland TJ (2008) Differential response to a selective cannabinoid receptor antagonist (SR141716: rimonabant) in female mice from lines selectively bred for high voluntary wheel-running behavior. Behav Pharmacol 19:812–820

Keeney BK, Meek TH, Middleton KM, Holness LF, Garland T Jr (2012) Sex differences in cannabinoid receptor-1 (CB1) pharmacology in mice selectively bred for high voluntary wheel-running behavior. Pharmacol Biochem Behav 101:528–537

Kim YP, Kim HB, Jang MH, Lim BV, Kim Y, Kim H, Kim SS, Kim EH, Kim CJ (2003) Magnitude- and time-dependence of the effect of treadmill exercise on cell proliferation in the dentate gyrus of rats. Int J Sports Med 24:114–117

Kirkcaldy BD, Shephard RJ (1990) Therapeutic implications of exercise. International Journal of Sport Psychology 21:165–184

Koltyn KF (2002) Exercise-induced hypoalgesia and intensity of exercise. Sports Med 32:477–487

Lieberman DE, Raichlen DA, Pontzer H, Bramble DM, C-S E (2006) The human gluteus maximus and its role in running. J Exp Biol 209:2143–2155

Lieberman DE, Bramble DM, Raichlen DA, Shea JJ (2007) The evolution of endurance running and the tyranny of ethnography: a reply to Pickering and Bunn (2007). J Hum Evol 53:439–442

Lieberman DE, Bramble DM, Raichlen DA, Shea JJ (2009) Brains, brawn, and the evolution of human endurance running capabilities. In: Grine F, Leakey REF (eds) The origin of homo. Plenum Press, New York, pp 77–92

Lou S, Liu J, Chang H, Chen P (2008) Hippocampal neurogenesis and gene expression depend on exercise intensity in juvenile rats. Brain Res 1210:48–55

Meng ID, Manning BH, Martin WJ, Fields HL (1998) An analgesia circuit activated by cannabinoids. Nature 395:381–383

Ogles BM, Masters KS (2003) A typology of marathon runners based on cluster analysis of motivations. J Sports Behav 26:69–85

Piomelli D (2003) The molecular logic of endocannabinoid signalling. Nat Rev Nuerosci 4:873–884

Raichlen DA, Foster AD, Gerdeman GL, Seillier A, Giuffrida A (2012) Wired to run: exercise-induced endocannabinoid signaling in humans and cursorial mammals and the evolution of the runner's high. J Exp Biol 215:1331–1336

Rasmussen EB, Hillman C (2011) Naloxene and rimonabant reduce the reinforcing properties of exercise in rats. Exp Clin Psychopharmacol 19:389–400

Reed J, Ones DS (2006) The effect of acute aerobic exercise on positive activated affect: a meta-analysis. Psychol Sport Exerc 7:477–514

Richardson JD (2000) Cannabinoids modulate pain by multiple mechanisms of action. J Pain 1:2–14

Sachs M, Pargman D (1979) Running addiction: a depth view. J Sports Behav 2:143–155

Solinas M, Justinova Z, Goldberg SR, Tanda T (2006) Anandamide administration alone and after inhibition of fatty acid amide hydrolase (FAAH) increases dopamine levels in the nucleus accumbens shell in rats. J Neurochem 98:408–419

Sparling PB, Giuffrida A, Piomelli D, Rosskopf L, Dietrich A (2003) Exercise activates the endocannabinoid system. Neuro Report 14:2209–2211

Tanaka H, Monahan KD, Seals DR (2001) Age-predicted maximal heart rate revisited. J Am Coll Cardiol 37:153–156

Vaughn LK, Denning G, Stuhr KL, Wit H, Hill MN, Hillard CJ (2010) Endocannabinoid signalling: has it got rhythm? Br J Pharmacol 160:530–543

Willoughby KA, Moore SF, Martin BR, Ellis EF (1997) The biodisposition and metabolism of anandamide in mice. J Pharmacol Exp Ther 282:243–247

Wolf SA, Bick-Sander A, Fabel K, Leal-Galicia P, Tauber S, Ramirez-Rodriguez G, Muller A, Melnik A, Waltinger TP, Ulrich O, Kempermann G (2010) Cannabinoid receptor CB1 mediates baseline and activity-induced survival of new neurons in adult hippocampal neurogenesis. Cell Commun Signal 8:12

Zoerner AA, Gutzki FM, Suchy MT, Beckmann B, Engeli S, Jordan J, Tsikas D (2009) Targeted stable-isotope dilution GC–MS/MS analysis of the endocannabinoid anandamide and other fatty acid ethanol amides in human plasma. J Chromatogr B Biomed Appl 877:2909–2923