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RESEARCH ARTICLE

Wired to run: exercise-induced endocannabinoid signaling in humans and cursorial mammals with implications for the 'runner's high'

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SUMMARY

Humans report a wide range of neurobiological rewards following moderate and intense aerobic activity, popularly referred to as the 'runner's high', which may function to encourage habitual aerobic exercise. Endocannabinoids (eCBs) are endogenous neurotransmitters that appear to play a major role in generating these rewards by activating cannabinoid receptors in brain reward regions during and after exercise. Other species also regularly engage in endurance exercise (cursorial mammals), and as humans share many morphological traits with these taxa, it is possible that exercise-induced eCB signaling motivates habitual high-intensity locomotor behaviors in cursorial mammals. If true, then neurobiological rewards may explain variation in habitual locomotor activity and performance across mammals. We measured circulating eCBs in humans, dogs (a cursorial mammal) and ferrets (a non-cursorial mammal) before and after treadmill exercise to test the hypothesis that neurobiological rewards are linked to high-intensity exercise in cursorial mammals. We show that humans and dogs share significantly increased exercise-induced eCB signaling following high-intensity endurance running. eCB signaling does not significantly increase following low-intensity walking in these taxa, and eCB signaling does not significantly increase in the non-cursorial ferrets following exercise at any intensity. This study provides the first evidence that inter-specific variation in neurotransmitter signaling may explain differences in locomotor behavior among mammals. Thus, a neurobiological reward for endurance exercise may explain why humans and other cursorial mammals habitually engage in aerobic exercise despite the higher associated energy costs and injury risks, and why non-cursorial mammals avoid such locomotor behaviors.

Key words: AEA, 2-AG, positive affect, running, walking, locomotion, *Homo*, exercise, endogenous cannabinoid.

INTRODUCTION

Goal-oriented behaviors that impose risks or high energy costs are often motivated by neurobiological rewards, which are thought to condition fitness-enhancing activities (Panksepp et al., 2002). Humans frequently report such neurobiological rewards (commonly termed the 'runner's high') during and after distance running that include 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). Central and peripheral rewards likely play a major role in humans' motivation to run (Ogles and Masters, 2003), and increase their ability to sustain high aerobic intensities over long distances (Dietrich and McDaniel, 2004). A neurobiological reward to encourage exercise may be especially important because high levels of aerobic activity are more energetically costly than walking (Cotes and Meade, 1960; Margaria et al., 1963; Menier and Pugh, 1968) and have a higher potential for both traumatic and overuse injuries (Johnson et al., 2000; Pinchbeck et al., 2004; Prole, 1976).

The hypothesis that neurobiological rewards motivate human endurance exercise (Ekkekakis et al., 2005; Sher, 1998) is consistent with evidence that humans are highly adept endurance athletes (Bramble and Lieberman, 2004; Carrier, 1984). For example, humans possess anatomical specializations and demonstrate endurance athletic performance (e.g. speed and distance traveled at aerobic intensities) that are similar to those of other mammals that habitually engage in endurance exercise, including long-distance running (i.e. cursorial mammals) (Bramble and Lieberman, 2004; Carrier, 1984). However, to date, no studies have examined the possibility that other cursorial mammals receive these same neurobiological rewards. This study tests the hypothesis that high levels of aerobic activity in humans and other cursorial mammals lead to neurotransmitter signaling associated with central and peripheral rewards. Additionally, we explore the possibility that inter-specific variation in exercise-induced rewards may play a role in the non-cursorial behaviors of some taxa.

Experimental research into these rewards is often hampered by the overall concept of the runner's high (see Dietrich and McDaniel, 2004), as it is often equated with generalized euphoric sensations in the popular press. Dietrich and McDaniel suggested a definition more amenable to hypothesis testing, where the runner's high is a change in any of the following observable phenomena: pain sensation, anxiolysis, sedation or feelings of well being (Dietrich and McDaniel, 2004). This definition includes quantifiable outcomes, allowing researchers to explore the neurobiological mechanisms that may be responsible for the runner's high. Recent work has supported a strong role for endocannabinoid (eCB) signaling in the rewards associated with endurance exercise (Dietrich and McDaniel, 2004). The two recognized eCBs, anandamide (AEA) and 2-arachidonylglycerol (2-AG), are endogenous ligands for the

CB_1 and CB_2 cannabinoid receptors, which were originally identified as the pharmacological targets of the principal psychoactive ingredient of marijuana, Δ^9-tetrahydrocannabinol (THC) (Piomelli, 2003). Because of high expression levels in brain regions relevant to affective processing, activation of CB receptors produces psychological rewards such as reduced anxiety, euphoria and a general feeling of well being (Piomelli, 2003).

The two eCBs (AEA and 2-AG) are released both centrally and peripherally in an activity-dependent manner to modulate the release of classical neurotransmitters (Piomelli, 2003). As a key example, eCBs released within the mesolimbic dopamine system lead to overall activation of dopamine neurons by relieving the influence of inhibitory, CB_1-expressing GABAergic terminals onto those neurons (Lupica and Riegel, 2005). This leads to enhanced dopamine release in target areas, such as the nucleus accumbens (NAc), a major brain area involved in behavioral reward (Cheer et al., 2007). Through this and perhaps other mechanisms intrinsic to the NAc, eCBs are thought to act as a 'hedonic' signal (Mahler et al., 2007), triggering neurobiological rewards that are similar to those described by runners (Dietrich and McDaniel, 2004), and which likely contribute to the development of habitual reward-directed behaviors (Gerdeman et al., 2003; Lupica and Riegel, 2005). In addition to these effects on neural systems of incentive within the brain, analgesic effects of eCBs occur both within the CNS and in the periphery, *via* CB receptors expressed on peripheral nerve fibers (Agarwal et al., 2007; Dietrich and McDaniel, 2004). Exercise-induced reductions in pain sensation lead to feelings of effortlessness associated with the strict definition of the runner's high and improve exercise performance by allowing individuals to run longer distances (Dietrich and McDaniel, 2004). Both the psychological and analgesic effects of CB receptor activation mirror athletes' descriptions of the neurobiological rewards associated with exercise (Dietrich and McDaniel, 2004).

Recent work supports direct links between eCB signaling and exercise in humans. Sparling and colleagues reported significant increases in plasma levels of AEA (but not 2-AG) after moderate-intensity aerobic activity (running or cycling at ~70–80% of maximum heart rate) (Sparling et al., 2003). Although their study measured plasma levels, eCBs are highly lipophilic, which allows them to readily cross the blood–brain barrier (Dietrich and McDaniel, 2004; Sparling et al., 2003). Thus, circulating levels of AEA or 2-AG are thought to lead to central effects because eCBs produced peripherally can cross the blood–brain barrier and activate CB receptors in brain reward centers (Dietrich and McDaniel, 2004; Solinas et al., 2006; Willoughby et al., 1997). Several studies have demonstrated this by showing that intravenous injections of eCBs (both AEA and 2-AG) activate CB receptors in the brain and lead to reward-seeking behaviors (e.g. self-administered injections) in animal models (Justinova et al., 2005; Justinova et al., 2011; Solinas et al., 2006; Willoughby et al., 1997).

Recent work in experimental evolution (i.e. selection experiments in rodents) suggests that eCB-induced rewards for exercise can be a target of natural selection and may explain habitual engagement in voluntary exercise in mammals. In female mice bred for high levels of voluntary wheel running over 15 years, administration of rimonabant (a selective CB receptor antagonist) led to significantly reduced levels of running compared with administration of a placebo, as well as with control mice given rimonabant (Keeney et al., 2008). Thus, selection used the eCB system to reward high amounts of voluntary running in these mice (Keeney et al., 2008), and these rewards encouraged increased levels of habitual voluntary exercise. However, it is unknown whether this system is linked to exercise in other mammals.

In this study, we measured plasma levels of eCBs in two cursorial species [humans (*Homo sapiens* L.) and dogs (*Canis familiaris* L.)] and one non-cursorial species [ferrets (*Mustela putorius* L.)] following 30 min of treadmill running to determine whether there is variation in exercise-induced eCB activity among mammals. On separate days, we measured plasma eCB levels in humans, dogs and ferrets after 30 min of low-intensity activity (treadmill walking for humans and dogs, resting for ferrets; see Materials and methods) to determine whether eCB signaling is intensity dependent. We predicted eCB signaling would be strongest following running, and should be stronger in humans and dogs than in ferrets.

MATERIALS AND METHODS

Our sample included recreationally fit humans (N=10), mixed-breed dogs (N=8) and ferrets (N=8) (see Table 1). Non-human taxa were chosen to match classical definitions of cursorial and non-cursorial evolutionary history based on morphological adaptations to endurance running (Jenkins, 1971). Humans and dogs were recruited from the local community. Only human subjects who were recreationally fit (i.e. could run 30 min continuously) were included in this study. Subjects received minimal treadmill training and experiments were conducted when subjects could run continuously at prescribed speeds for 30 min. The period of training for both dogs and ferrets ranged from one to three sessions and consisted only of positive reinforcement methods. All methods were approved by the University of Arizona IACUC and IRB.

Running speed for human subjects (see Table 1) was selected to elicit heart rates similar to those used previously (Sparling et al., 2003). Walking speed in humans was selected to match preferred walking speed as calculated by Froude number [velocity^2/(hindlimb length $\times$ gravitational acceleration)$\approx$0.25 at preferred walking speed), a dimensionless speed that accounts for differences in body size among subjects (see Table 1) (Alexander and Jayes, 1983; Minetti, 2001). While Froude numbers of 0.25 roughly correspond to preferred walking speed (Minetti, 2001), we note that this was not self-selected by subjects but was calculated based on each subject's anatomy. Heart rate for running speed averaged 72.5±2.54% (mean ± s.d.) of maximum heart rate and walking speed corresponded to a mean (±s.d.) of 44.6±1.25% of maximum heart rate [where maximum heart rate was calculated using the age-based equation from Tanaka et al. (Tanaka et al., 2001)]. Heart rates for running trials are well below the ventilatory threshold (the transition from aerobic to anaerobic exercise) known to influence

Table 1. Subject data

Taxon	Body mass (kg)	Walking speed (m s^{-1})	Running speed (m s^{-1})	Walking Froude	Running Froude
Humans	67.35±9.06	1.25	2.5	0.26±0.01	0.71±0.03
Dogs	28.11±7.68	1.10±0.047	1.83±0.8	0.25	0.70
Ferrets	1.12±0.15	0.50±0.01	0.84±0.01	0.25	0.70

Mean values are shown ±s.d.

psychological responses to exercise (Ekkekakis et al., 2004). Speed for non-human runners was chosen to match Froude numbers used by human subjects, such that subjects all walked and ran at dynamically similar speeds. All subjects (humans, dogs and ferrets) ran at Froude numbers of ~0.70 for 30 min (trotting gaits for ferrets and dogs). Dogs and humans walked at Froude numbers of ~0.25 for 30 min. Ferrets were unable to walk consistently on the treadmill at any speed, so we compared data from running trials with data collected after a 30 min control trial where ferrets sat quietly in a small cage.

Blood samples (0.5 ml) were collected by venipuncture before and after each of these trials using a syringe filled with 1 ml of Krebs-Tris buffer/EDTA (4.5 mmol l^{-1}). Samples were immediately centrifuged in Accuspin tubes (Sigma, St Louis, MO, USA) at 800 ***g***, for 10 min. Methods for eCB extraction (both AEA and 2-AG) and quantification by GC/MS isotope dilution are described in detail elsewhere (Hardison et al., 2006).

Psychological state was assessed before and after all human trials using a standard questionnaire that measures positive affect [positive and negative affect schedule (PANAS) scale (Watson et al., 1988)]. Positive affect (PA) describes the enthusiasm, energy and pleasurable engagement of an individual (Watson et al., 1988), and is an important component of feelings of well being (Reed and Ones, 2006). As with many psychological instruments, there are limitations to the PANAS that should be taken into account when interpreting our results. For example, researchers have suggested that this scale is limited to only the high activation ends of PA (e.g. excited or enthused) (see Egloff, 1998; Mossholder et al., 1994; Russell and Carroll, 1999). Thus, the low-activation ends of PA (e.g. calm or serene) may not be fully captured using this instrument. Despite this limitation, the PANAS has been used in many previous studies to effectively capture exercise-related changes in affect (Reed and Ones, 2006).

Subjects performed only one trial per day. Because day-to-day fluctuations in baseline eCB levels are normal and 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. Differences between AEA and 2-AG levels before and after exercise were assessed using paired *t*-tests. A Pearson product-moment correlation was calculated between the post- and pre-exercise difference in eCBs and the post- and pre-exercise difference in PA.

RESULTS

Both humans and dogs showed a significant increase in plasma levels of AEA following a 30 min treadmill run; however, neither taxon showed increased AEA levels following a lower intensity 30 min walk (dogs showed a significant decrease in AEA following walking trials; see Fig. 1 and Table 2). In ferrets, plasma AEA levels were unchanged following either a 30 min run or a 30 min rest period (see Fig. 1 and Table 2, and Materials and methods). Similar to Sparling and colleagues' (Sparling et al., 2003) results in humans, no taxon showed a significant change in levels of 2-AG following any exercise trial (Table 2). The difference between pre- and post-exercise levels of AEA in humans was positively correlated with the difference between pre- and post-exercise PA (r=0.96, P<0.0001; Fig. 2). The correlation remained significant after removing the possible outlier (highest AEA and PA change; r=0.77, P<0.05).

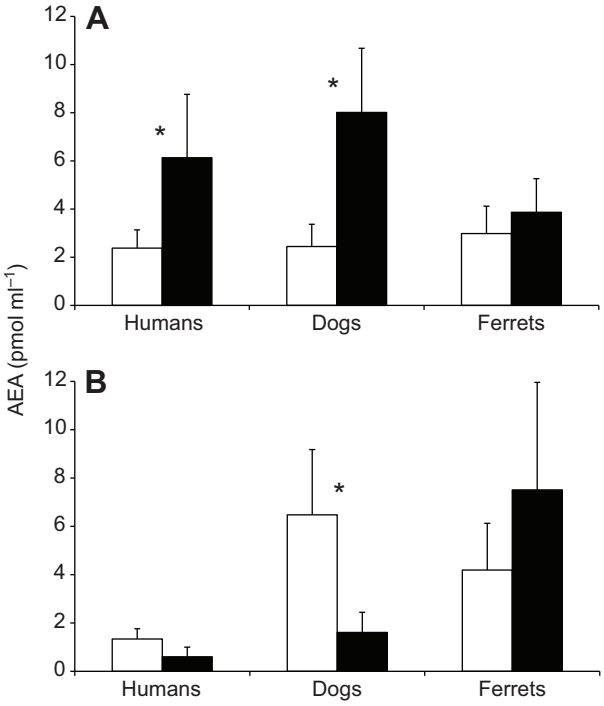

Fig. 1. Changes in anandamide (AEA) concentrations before and after treadmill exercise. Pre-exercise levels are shown in white; post-exercise levels are shown in black. (A) Plasma AEA levels before and after running for 30 min at a Froude number of 0.70. (B) Plasma AEA levels before and after walking for 30 min at a Froude number of 0.25. Asterisks indicate significant differences at P<0.05. Error bars are s.e.m.

DISCUSSION

This is the first study to show that there is inter-specific variation in neurotransmitter signaling following exercise and that this variation may explain differences in habitual locomotor behaviors among mammals. In humans and dogs, but not ferrets, running activates the eCB system, which likely improves aerobic exercise performance and encourages a high frequency of aerobic activity in these cursorial taxa. In humans, increased eCB signaling following exercise is significantly correlated with improved PA, confirming the role of eCBs in generating positive psychological effects. eCB signaling does not increase following low-intensity activity in humans and dogs, suggesting that these rewards are not simply triggered by locomotion but are tied to higher exercise intensities. In fact, eCB levels decreased in dogs following the 30 min walking trial. This result suggests that dogs may not have any specific affective response to walking under these experimental conditions. In ferrets, a taxon that does not generally engage in cursorial activity (see King and Powell, 2007), and is not morphologically adapted to endurance exercise behaviors (Jenkins, 1971), exercise does not result in an increase in eCB signaling. This inter-specific variation suggests that eCB signaling plays a functional role in the aerobic behaviors of cursorial mammals.

eCBs can aid cursorial mammals by improving high-intensity athletic performance through both central and peripheral actions. Centrally, CB receptors are primarily expressed in presynaptic terminals, where activation by eCBs leads to a decrease in the synaptic release of classical neurotransmitters (Piomelli, 2003) and produces psychological effects similar to those described by runners in this study (Chaperon and Thiebot, 1999; Diaz, 1997; Piomelli, 2003). It is important to note that this study measured peripheral eCB levels only, and thus we cannot be sure that our measurements fully reflect changes in eCBs within the central nervous system. However, the strong correlation between changes in AEA and

Table 2. Pre- and post-exercise values of AEA and 2-AG

			AEA			2-AG		
Speed	Taxon	*N*	Pre-exercise (pmol ml^{-1})	Post-exercise (pmol ml^{-1})	*P*-value	Pre-exercise (nmol ml^{-1})	Post-exercise (nmol ml^{-1})	*P*-value
Walk/control	Human	10	1.34±0.43	0.61±0.39	0.10	0.004±0.0001	0.021±0.002	0.16
	Dog	8	6.48±2.7	1.61±0.83	**0.04**	0.039±0.019	0.124±0.055	0.10
	Ferret	8	4.19±1.93	7.51±4.45	0.14	0.049±0.009	0.032±0.013	0.25
Run	Human	10	2.38±0.76	6.13±2.63	**0.03**	0.007±0.005	0.029±0.022	0.19
	Dog	8	2.44±0.92	8.01±2.66	**0.03**	0.056±0.018	0.268±0.201	0.17
	Ferret	8	2.98±1.13	3.87±1.39	0.33	0.428±0.218	0.229±0.118	0.31

AEA, anandamide; 2-AG, 2-arachidonylglycerol.
Mean values are shown ±s.e.m.
Bold values are significant differences found using a paired *t*-test.

changes in PA following exercise shown here (Fig. 2) suggests that post-running AEA levels measured peripherally in plasma are reflective of increased AEA in the central nervous system (Dietrich and McDaniel, 2004). This is possible because eCBs are highly lipophilic and physiological studies suggest that they 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; Justinova et al., 2011; Solinas et al., 2006; Willoughby et al., 1997).

Improvements in PA such as those measured here are a major factor in human runners' motivation to habitually engage in aerobic exercise (Bryan et al., 2007; Kwan and Bryan, 2010; Schneider et al., 2009; Williams et al., 2008), suggesting that one role for eCB-induced rewards is to encourage a high frequency of aerobic activity. These effects are not limited to elite athletes. Many studies have shown that aerobic exercise has a positive psychological effect in healthy populations of non-athletes (Reed and Ones, 2006), and the improvements in mood and PA play a role in how well individuals adhere to exercise programs (Ekkekakis et al., 2005). Additionally, exercise improves psychological well being in non-athletic individuals with depressive or anxiety disorders (Scully et al., 1998). Thus, these broadly felt rewards are likely essential for the enjoyment of exercise and may explain why mammalian taxa engage in cursorial behaviors despite the higher energy costs and associated injury risks (Bramble and Lieberman, 2004; Johnson et al., 2000; Pinchbeck et al., 2004; Prole, 1976).

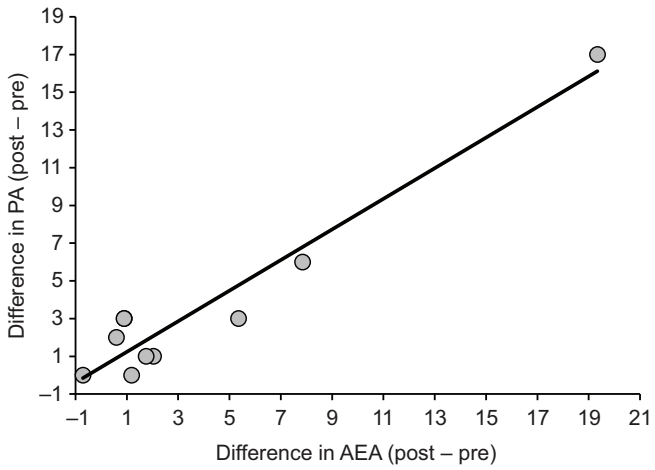

Fig. 2. Correlation between positive affect (PA) and AEA in humans. Values are the difference between pre- and post-exercise PA scores plotted against the difference between pre- and post-exercise plasma levels of AEA. Note that the values for two subjects were nearly identical (difference in AEA=0.89 and 0.90, difference in PA=3 for both subjects), and they are not differentiated on the figure.

In addition to central effects on psychological state, eCBs may act at peripheral CB receptors to decrease nociceptor activity (Agarwal et al., 2007) and produce exercise-induced analgesia (Sparling et al., 2003). This reduction in pain sensitivity is an important component of the runner's high (i.e. feelings of effortlessness) as defined by Dietrich and McDaniel (Dietrich and McDaniel, 2004), and one that improves aerobic exercise performance by allowing individuals to continue running for long distances. Exercise-induced analgesia is a widespread phenomenon that occurs in both athletes and non-athletes following moderate and high-intensity exercise (Hoffman and Hoffman, 2007; Koltyn, 2002). eCBs reduce pain throughout the body because peripheral nerves that are active in sensing pain pathways contain dense concentrations of CB receptors (Dietrich and McDaniel, 2004), which function to inhibit the release of neurotransmitters (Gerdeman, 2008; Piomelli, 2003). Peripheral analgesia by eCBs is also achieved through the actions of CB receptors to inhibit the release of inflammatory mediators (Hohmann and Suplita, 2006; Ibrahim et al., 2003). In addition to acting at peripheral sites, CB receptors are found at central sites implicated in pain modulation such as the dorsal horn of the lumbar spinal cord and the rostral ventromedial medulla of the brainstem (Hohmann et al., 1999; Meng et al., 1998), suggesting that circulating eCBs may also lead to a central reduction in pain perception.

Thus, the measured increases in AEA levels in the circulating bloodstream likely produce both peripheral (i.e. analgesic) and central effects that support their role in encouraging aerobic activity and improving exercise performance (Dietrich and McDaniel, 2004). As eCBs function similarly across mammals (Chaperon and Thiebot, 1999), our results suggest that both humans and dogs achieve a psychological and physiological benefit from increased AEA signaling during and after running. The intensity-dependent nature of eCB activity in humans and dogs suggests that neurobiological rewards function to encourage higher exercise intensities than those required at walking speed.

CONCLUSIONS

Exercise-induced eCB signaling increases following higher intensity aerobic activities in humans and dogs, but not in the non-cursorial ferrets. This study is the first to explore inter-specific variation in

exercise-induced neurotransmitter signaling and, thus, represents a novel method for examining how and why mammals engage in different types of locomotor behaviors. Our results show that neurobiological differences among mammalian taxa may explain variation in their habitual locomotor behaviors.

Although this study is based on a limited taxonomic sample, we believe that our results point to a possible neurobiological explanation for how different locomotor behaviors may evolve. The shared exercise-induced eCB signaling pathway in humans and dogs, but not in the non-cursorial ferrets, is consistent with anatomical and biomechanical studies pointing to selection for increased levels of aerobic activity in humans (Bramble and Lieberman, 2004; Carrier, 1984). It is important to interpret the results of this study in the context of previous work showing that human endurance exercise performance matches that of mammals traditionally defined as cursorial (Bramble and Lieberman, 2004; Carrier, 1984). For example, humans can habitually run distances and at speeds comparable to other cursorial mammals, and humans share many anatomical traits with quadrupedal cursors that improve endurance athletic performance (e.g. increased limb length, increased semi-circular canal size, increased joint surface areas) (Bramble and Lieberman, 2004; Carrier, 1984). Our results show that humans also share a neurobiological trait with a cursorial mammal that improves endurance exercise performance and may explain the known psychological benefits and analgesic effects of exercise in humans (Dietrich and McDaniel, 2004; Scully et al., 1998). Given evidence from recent experiments that the eCB system is a target of selection which encourages exercise in mammals that undergo experimental evolution for high levels of voluntary running (Keeney et al., 2008), we suggest that eCB signaling represents a possible evolutionary explanation for the neurobiological rewards associated with exercise in humans.

Our study does have some limitations that should be noted when interpreting our results. First, we measured eCB signaling in a relatively small number of taxa. Thus, we suggest that future studies analyze a larger number of non-cursorial and cursorial taxa to fully understand the variation in exercise-induced neurobiological rewards across mammals. Second, our experiments did not test for a specific mechanical trigger of eCB signaling. Although we used running behaviors to determine exercise-induced eCB signaling across taxa, Sparling and colleagues showed that eCBs are released in humans following both cycling and running at moderate aerobic intensities (Sparling et al., 2003). Neurobiological rewards are likely tied to high levels of endurance activity, but may not be triggered by a specific mechanical behavior *per se*. From an evolutionary perspective, these levels of aerobic activity are likely achieved in different taxa during high-intensity running behaviors, suggesting selection may have acted to encourage these intensities during legged locomotion. Third, our human sample was made up of recreationally fit subjects; however, we do not know whether our results are generalizable to more sedentary human populations. We suggest that, for tests of evolutionary hypotheses, fit individuals make better models of earlier human groups, as our ancestors lived active hunter–gatherer lifestyles (Malina and Little, 2008). Nonetheless, further research examining the role of fitness level in eCB activity in humans is necessary. It is possible that more sedentary groups cannot adequately exercise at the intensities required to elicit a significant eCB elevation, and do not gain similar psychological benefits from exercise at lower intensities. This possible intra-specific variation in physical fitness may explain why some individuals do not enjoy exercise. Finally, while we showed that eCB activity is correlated with PA, and therefore feelings of well being in our human sample, we did not measure other aspects of the runner's high as defined by Dietrich and McDaniel (Dietrich and McDaniel, 2004). While eCB activity is linked to reductions in pain sensitivity, anxiolysis and sedation (Piomelli, 2003; Dietrich and McDaniel, 2004), future work should examine these traits in more detail to determine whether exercise-induced eCBs lead to changes in all aspects of the runner's high.

Despite these limitations, our results lay the foundation for a more thorough understanding of the psychological and physiological effects of exercise in cursorial mammals, including humans. It is possible that neurobiological rewards induced by eCB signaling are an ancient human trait that evolved to encourage aerobic activity (Bramble and Lieberman, 2004; Carrier, 1984; Malina and Little, 2008), and that the rewards explain the evolution of differences in voluntary locomotor activity more broadly across mammals. Future studies are needed to fully support this evolutionary hypothesis; however, our results provide the framework for a novel way to examine the evolution of endurance exercise in humans and other mammals. The fact that running, and endurance exercise in general, remains an enjoyable and psychologically beneficial recreational activity for tens of millions of humans today suggests that we still may respond to a neurobiological trait that evolved early in our lineage.

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