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# Intense exercise increases circulating endocannabinoid and BDNF levels in humans—Possible implications for reward and depression

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**Summary** The endocannabinoid system is known to have positive effects on depression partly through its actions on neurotrophins, such as Brain-Derived Neurotrophic Factor (BDNF). As BDNF is also considered the major candidate molecule for exercise-induced brain plasticity, we hypothesized that the endocannabinoid system represents a crucial signaling system mediating the beneficial antidepressant effects of exercise. Here we investigated, in 11 healthy trained male cyclists, the effects of an intense exercise (60 min at 55% followed by 30 min at 75% $W_{max}$) on plasma levels of endocannabinoids (anandamide, AEA and 2-arachidonoylglycerol, 2-AG) and their possible link with serum BDNF. AEA levels increased during exercise and the 15 min recovery ($P < 0.001$), whereas 2-AG concentrations remained stable. BDNF levels increased significantly during exercise and then decreased during the 15 min of recovery ($P < 0.01$). Noteworthy, AEA and BDNF concentrations were positively correlated at the end of exercise and after the 15 min recovery ($r > 0.66$, $P < 0.05$), suggesting that AEA increment during exercise might be one of the factors involved in exercise-induced increase in peripheral BDNF levels and that AEA high levels during recovery might delay the return of BDNF to basal levels. AEA production during exercise might be triggered by cortisol since we found positive correlations between these two compounds and because corticosteroids are known to stimulate endocannabinoid biosynthesis. These findings provide evidence in humans that acute exercise represents a physiological stressor able to increase peripheral levels of AEA and that BDNF might be a mechanism by which AEA influences the neuroplastic and antidepressant effects of exercise.


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## 1. Introduction

Chronic physical exercise has beneficial effects on the ''depressive-like'' phenotype and involves changes in adult neurogenesis with possible impact on reward and cognitive behavior (Ernst et al., 2006; Dishman et al., 2006; Brene et al., 2007). Up to date, Brain-Derived Neurotrophic Factor (BDNF), a member of the neurotrophin family promoting neuronal survival and proliferation (Castren and Rantamaki, 2010), has been described as one of the best potential candidate molecules playing a role in exercise-induced antidepressant effects (Duman et al., 2008; Li et al., 2008), particularly through promotion of neurogenesis (Lafenetre et al., 2010; Erickson et al., 2011). Recent data underline the putative role of the endocannabinoid system in the etiology of depression. Thus, the two most studied endocannabinoids, *N*-arachidonoylglycerol (anandamide, AEA) and 2-arachidonoylglycerol (2-AG), which are synthesized on demand in various central and peripheral tissues, have the capacity, through their agonist effects on the cannabinoid CB1 receptor, to alter cognitive and emotional behaviors, neurogenesis, and the levels of neurotrophins, such as BDNF (Gorzalka and Hill, 2010). These behaviors and molecules are also influenced by physical exercise, and one could speculate that the endocannabinoid system represents a crucial signaling system mediating the beneficial antidepressant effects of exercise. In addition to its putative antidepressant effects, the endocannabinoid system may acutely influence mood through its effects on pain perception (Pertwee, 2001) and its facilitation of dopamine release in the nucleus accumbens (Maldonado et al., 2006; Cheer et al., 2007). Endocannabinoids have thus been hypothesized to be linked with the so-called ''runners high'', an intense but transient positive emotion during exercise (Dietrich and McDaniel, 2004; Keeney et al., 2008; Fuss and Gass, 2010; Garland et al., 2011).

To date, only one human study has investigated the specific effects of exercise on plasma endocannabinoid levels in humans, although without dealing with correlates of cognitive or emotional function (Sparling et al., 2003). The authors observed a significant increase of plasma AEA but not 2-AG in trained subjects following a 45-min acute exercise (Sparling et al., 2003). Unfortunately, the exercise intensity was not individualized for each subject and the exercise was performed at different times from the last non-standardized meal, between 14.00 and 17.00 h. This lack of method standardization might have influenced the results since the variability of exercise intensity is reflected into the level of stress (Urhausen et al., 1995) and the differences of quantity and quality of food and of the time-lag from the last meal might influence the endocannabinoid levels (Di Marzo and Matias, 2005).

Few other studies used rodents to investigate the effects of exercise on endocannabinoid signaling, specifically in the brain. Authors showed that 15 days, 10 days, or eight days of free access to running wheels sensitized the CB1 receptor-mediated responses in the striatum (De Chiara et al., 2010), increased the expression of CB1 receptor mRNA in the hippocampus (Wolf et al., 2010), or increased CB1 receptor binding and intrinsic activity and AEA levels in hippocampus (Hill et al., 2010a), respectively.

Four recent animal studies addressed the question as to whether the exercise-induced modification of endocannabinoid signaling mediates wheel-running-induced effects on depression by correlating with, e.g. neurogenesis (Dubreucq et al., 2010; Hill et al., 2010a; Wolf et al., 2010) or stress-induced anxiety (De Chiara et al., 2010). In three of such studies, it was suggested that modification of endocannabinoid signaling may represent a crucial factor in exercise-induced neurogenesis (Hill et al., 2010a; Wolf et al., 2010) and stress coping (De Chiara et al., 2010). However, caution should be taken when extrapolating to humans the results of these animal studies, in which pharmacological and genetic approaches were used. These approaches have the usual disadvantages of systemic applications and congenital alterations, possibly inducing basal neurohormonal alterations (Steiner and Wotjak, 2008) and not necessarily representative of local physiological changes induced by exercise. Furthermore, although wheel-running is voluntary, the time and frequency spent exercising differ between rodents and humans, since, in humans, voluntary training sessions consist of acute, often single, daily bouts of exercise. Most importantly, free access to wheel running represents not only a voluntary exercise, but also the opportunity of being an enriched environment, two environmental conditions known to act positively on neurogenesis (Will et al., 2004). The observation of a specific role of exercise may be overestimated by the presence of the enriched environment.

Based on this background, the purpose of the current study was to examine, in an homogeneous group of cyclists, the effect of a well-standardized exercise on the plasma levels of the two most studied endocannabinoids (2-AG, AEA), and of the two AEA congeners with activity at peroxysome proliferator-activated receptor-$\alpha$ (PPAR-$\alpha$) [*N*-oleylethanolamine (OEA) and *N*-palmitoylethanolamine (PEA)], and their possible link with BDNF, the major candidate molecule for exercise-induced brain plasticity. Other factors such as $\beta$-endorphins, which might also play a role and synergize with endocannabinoids in reward (Trezza et al., 2011) and cortisol, which stimulates endocannabinoid biosynthesis and is down-regulated by CB1 in the brain (Hill et al., 2010b), were also measured. The exercise protocol and the time intervals of blood sampling used in this study allowed to investigate the effects of two individualized intensities of exercise and the impact of the duration of exercise as well as of the recovery phase.

## 2. Methods

### 2.1. Subjects

Eleven young well-trained male cyclists [age $23.3 \pm 5.1$ (SD) yr, body mass $77.4 \pm 8.3$ (SD) kg, height $1.83 \pm 0.07$ (SD) m] participated in the study. All subjects gave written informed consent after receiving information regarding the nature and purpose of the experimental protocol. The study was approved by the ethical committee of the Vrije Universiteit Brussel, Belgium.

### 2.2. Study design

No exercise practice, alcohol, coffee were permitted in the 24 h before each exercise. All subjects were non-smokers.