Endocannabinoids and exercise

A Dietrich, W F McDaniel

Exercise induces changes in mental status, particularly analgesia, sedation, anxiolysis, and a sense of wellbeing. The mechanisms underlying these changes remain unknown. Recent findings show that exercise increases serum concentrations of endocannabinoids, suggesting a possible explanation for a number of these changes. This article provides an overview of this emerging field.

A n exercise induced altered state of consciousness has long been appreciated by endurance athletes. The effect has been well documented in the popular literature and subjected to scientific investigation.3 In the late 1960s, the psychological changes associated with prolonged physical activity were often described as a “second wind.” 4 A more contemporary label often applied to these exercise induced changes is the “runner’s high.” The runner’s high has been described subjectively as pure happiness, elation, a feeling of unity with one’s self and/or nature, endless peacefulness, inner harmony, boundless energy, and a reduction in pain sensation. 5–7 These subjective descriptions are similar to the claims of distorted perception, atypical thought patterns, diminished awareness of one’s surroundings, and intensified introspective understanding of one’s sense of identity and emotional status made by people who describe drug or trance states.

As is the case with all phenomena related to consciousness and its alterations, the runner’s high is a private experience, and the evidence for its existence rests predominantly on verbal report. Scientific inquiry into the phenomenon has been restricted even further because of its ephemeral nature. For example, the runner’s high is not experienced by all runners, and this experience does not occur consistently in runners who have experienced it previously. These observations have left laymen and scientists wondering why and under which conditions the runner’s high occurs, or whether or not it exists at all.

Before the discovery of the opioids, exercise scientists tried to account for the analgesic and euphoric mental states with alterations in the catecholamines adrenaline (epinephrine) and noradrenaline (norepinephrine). 8 With the discovery and subsequent characterization of the opioid receptor network and endogenous opioid peptides, an entirely different mechanism of action evolved. Soon thereafter, exercise induced changes in psychological functions were often described as being a direct consequence of alterations in endogenous opioid release. However, there are a number of serious problems with the “endorphin hypothesis.” 9–11 Studies examining the exercise-endorphin connection produced equivocal results, and many of the studies were plagued by methodological confounds. For instance, β endorphin has almost the same amino acid sequence as other members of the pro-opiomelanocortin family such as the adrenocorticotropic hormone, making cross reactivity to the detecting antibody a serious confound. Also, adrenocorticotropic hormone is a stress hormone that is known to increase with exercise, compounding the problem. There are also major inconsistencies between the endorphin hypothesis and the physiological and biochemical responses to endurance exercise. For instance, β endorphins bind best to the µ opioid receptor, the endogenous opioid system that mediates the analgesic and euphoric properties of the opiates. However, minimal activation of the same endogenous opioid system is also responsible for the severe respiratory depression, pinpoint pupils, and inhibition of gastrointestinal motility, all of which accompany opiate use. Yet, these effects are not seen in runners. The most limiting factor, however, is that the endorphin hypothesis rests entirely on research measuring endorphins in circulating blood, as ethical reasons preclude the determination of central concentrations of endorphins. Because endorphins are too large to cross the blood-brain barrier, peripheral activation in the systemic circulation cannot be taken as indicative of central effects. In recent years, several prominent endorphin researchers—for example, Dr Huda Akil and Dr Solomon Snyder—have publicly criticised the hypothesis as being “overly simplistic”, being “poorly supported by scientific evidence”, and a “myth perpetrated by pop culture.” 11

At first glance, it appears that the runner’s high phenomenon is, at present, not a scientific problem because it is built on circumstantial evidence and lacks a plausible mechanistic explanation. However, recent data in our laboratory showed that endurance exercise activates the endocannabinoid system, 12 suggesting a new mechanism underlying exercise induced alterations of mental status. Using trained male college students running on a treadmill or cycling on a stationary bike for 50 minutes at 70–80% of maximum heart rate, we found that exercise of moderate intensity dramatically increased concentrations of anandamide in blood plasma. (Currently, research is underway in our laboratory to explore this finding further by examining

Abbreviations: 2-AG, sn-2-arachidonylglycerol; THC, tetrahydrocannabinol
the effect of exercise on both serum and cerebrospinal fluid concentrations of endocannabinoids in exercising rats, while also examining several associated alterations of behaviour.) Because activation of the endocannabinoid system reduces pain sensations and alters emotional and cognitive processes, this finding has implications for some of the psychological effects that accompany exercise. Owing to the presence of cannabinoid receptors in muscle, skin, endothelial cells, and lung, this finding also suggests a possible role for the endocannabinoid system in mediating certain physiological responses to exercise.

It is important to emphasize that the intention of this paper is not to substitute one neurotransmitter for another and perpetuate the simple reductionist idea of one neurochemical being responsible for a complex variety of psychological processes. Rather, we review the literature on the functional role of the endocannabinoid system as it relates to exercise and call attention to the possibility that the endocannabinoid system may play an important role in the physiological and psychological adaptations to exercise. The review opens unexpected and entirely novel avenues of research in exercise physiology and psychology and is offered on the strength of its heuristic value.

In addition, we propose to reconceptualise the runner's high into a set of behavioural phenomena that can be, at least to a large extent, subjected to scientific scrutiny. Traditional concepts of the runner's high have been operationalised as a "euphoric sensation experienced during running, usually unexpected, in which the runner feels a heightened sense of well being, enhanced appreciation of nature, and transcendence of barriers of time and space" (Pargman et al p 342). It is obvious that such a broad definition, in conjunction with the extensive use of esoteric language, does not qualify as an operational definition that can be used to derive testable hypotheses. We propose instead a more limited operational definition of the runner's high centred mostly on observable behaviours such as analgesia, sedation (post-exercise calm), anxiolysis, and a sense of wellbeing. This definition has a number of advantages. Firstly, there is a large body of scientific literature documenting that exercise suppresses pain, induces sedation, reduces stress, and elevates mood. Secondly, because these effects are directly measurable, the operational definition allows the formulation of empirical predictions and the testing of specific hypotheses. Moreover, data from animal research can be recruited to elucidate the phenomena, as exercise in rodents has been shown to increase tolerance of pain (hot plate or tail flick tests), induce sedation (open field test), and produce anxiolysis (elevated plus maze).

**THE ENDOCANNABINOID HYPOTHESIS**

Endocannabinoid receptors and their endogenous ligands have been identified. To date, two cannabinoid receptor subtypes have been cloned. The CB₁ receptor is located in the central nervous system, and it is more densely concentrated on the membranes of neurons located in the cortex, hippocampus, basal ganglia, amygdala, hypothalamus, and cerebellum. CB₁ receptors are also found in several peripheral sites, including the peripheral nervous system. The CB₂ receptor, on the other hand, is located mainly in peripheral tissue. Both the CB₁ and CB₂ receptors are coupled to Gi/o proteins. Thus cannabinoid receptors inhibit adenylate cyclase and, thereby, depending on the cell type, either inhibit voltage gated calcium channels or activate potassium channels. Thus, with respect to the nervous system, the general effect of CB₁ activation is neuronal inhibition, which does not apply to CB₂ receptors, as they are mainly expressed on immune cells. There is also an ongoing hypothesis in the field that there may exist an additional cannabinoid receptor, tentatively named CB₃. Although the existence of a CB₃ receptor is currently hypothetical, it may be of interest as some of the effects reported in this review might turn out not to be accounted for by CB₁ and CB₂ receptors.

Two naturally occurring ligands, which are members of a small family of fatty acid derivatives, have been identified for CB₁ and CB₂ receptors. Anandamide is one ligand, and it exhibits a higher affinity for the CB₁ receptor subtype than CB₂. A second ligand, sn-2-arachidonoylglycerol (2-AG), has been identified more recently. Although the two endocannabinoids are found in the systemic circulation at equal concentrations, the concentration of 2-AG is about 200 times higher than that of anandamide in the brain. Anandamide and 2-AG have different biosynthetic pathways and may be produced under different conditions. However, the sites of anandamide and 2-AG production in brain and peripheral tissues are not known. Because endocannabinoids are lipids that are rapidly eliminated from extracellular space, it is generally assumed that production sites are located in close proximity to their attending cannabinergic receptors. More importantly, the environmental stimuli responsible for the production and release of endocannabinoids are also unknown, making it difficult to assess the physiological and behavioural functions of anandamide and 2-AG.

**Cannabinoids and exercise induced analgesia**

The role of the endocannabinoid system as an alternative neuromodulatory system in pain perception has been a central focus of cannabinoid research. Analgesia is mediated in part by the endogenous opioid system. However, analgesia that is insensitive to opioid antagonists can also occur, providing evidence for non-opioid antinociception. Using animal models of acute and tonic pain, behavioural studies with a wide variety of noxious stimuli have shown cannabinoid induced antinociception, which is mediated by CB₁ receptors. The potency and efficacy of cannabinoids in producing antinociception rivals that of morphine.

Unlike opioid mediated suppression of pain neurotransmission, the endocannabinoid system has been shown to suppress pain not only at central, but also at peripheral concentrations. CB₁ receptors are densely expressed on peripheral nerve terminals such as pain sensing C (small diameter) fibres, large diameter Aβ and Aδ fibres, as well as in the dorsal root ganglia. Cannabinoids also act at central sites to modulate pain sensation. For example, cannabinoid receptors in the dorsal horn of the lumbar spinal cord have been shown to attenuate pain evoked by noxious heat applied to rat hind paw. In the brain, Meng et al found a brainstem circuit involving the rostral ventromedial medulla that is activated by cannabinoids. Although activation of neurones in the rostral ventromedial medulla is also required for the analgesic effects of morphine, the cannabinoids modulate its activity independently, demonstrating a separate central mechanism of action for antinociception. The cannabinoids also affect pain perception by acting in the periaqueductal gray system, an area dense in opioid receptors. Electrical stimulation of the dorsal and lateral periaqueductal gray system produces analgesia that is both CB₁ receptor mediated and accompanied by the release of anandamide in the system. Finally, subcutaneous injection of the chemical irritant formalin triggers an increase of anandamide in the periaqueductal gray system, further implicating the endocannabinoids not only in the modulation of chemogenic pain, but also more generally in the centrally mediated suppression of pain. Cannabinoids and opioids also exhibit synergistic effects in the production of antinociception, and bidirectional interactions between opioid and cannabinoid dependence have been reported. For example, administration of naltroxone, a μ opioid
receptor antagonist, induces withdrawal in cannabinoid dependent rats, whereas administration of the CB1 receptor antagonist SR141716A precipitates withdrawal in morphine dependent rats.46

With regard to exercise induced analgesia, there are some significant differences between opioid and cannabinoid antinociception. Firstly, cannabinoids produce analgesia by acting at a number of peripheral sites.14 15 Although endo-cannabinoids such as anandamide are lipids and can cross the blood-brain barrier readily, this is not a requirement for the analgesic properties of endocannabinoids. This fact avoids one of the principal problems that plagued the endorphin hypothesis of exercise induced analgesia. Secondly, because of its highly lipophilic properties, systemic increases in anandamide concentrations are generally assumed to produce central effects. Consequently, in addition to peripheral sites, the increase in blood anandamide concentrations in endurance athletes is likely to activate analgesic systems in the brain. Finally, as mentioned above, subcutaneous injections of the chemical irritant formalin into rat hind paw increases the release of anandamide in the periaqueductal gray system,39 showing that noxious agents can produce analgesia at central sites without the activation of peripherally circulating endocannabinoids.

Research on cannabinoid induced analgesia has made use of a variety of noxious stimuli, and it has become clear that different types of tissue damage (mechanical, thermal, chemical, etc) differentially activate the endocannabinoid system.14 19 The finding that there are particular types of pain against which cannabinoids are particularly effective may provide fresh insights into the sport specificity of the runner’s high. It is curious that an “exercise high”, similar to the one experienced by long distance runners, should not occur in sports requiring changes in pace and workload such as track, soccer, football, tennis, basketball, etc. Further testing should resolve the issue as to whether these activities engage the endocannabinoid system.14 19 The finding that there are particular types of pain against which cannabinoids are particularly effective may provide fresh insights into the sport specificity of the runner’s high.

Psychoactive effects of cannabinoids

The psychoactive constituent of marijuana, Δ(9)-tetrahydrocannabinol (THC), exhibits high affinity for the CB1 receptor, which is densely expressed in brain regions implicated in the control of emotion and cognition.29 62 This distribution provides the basis for the profound psychological effects of exogenous cannabinoids. A prominent effect of cannabinoids is the induction of sedation.15 In addition, cannabinoids are reported to reduce anxiety,45 63 alter attention,45 and impair both working memory46 and spatial learning,47 48 apparently by interfering with hippocampus dependent neuronal processes responsible for declarative memory.26 Users of marijuana often report distortions of time estimation,50 euphoria and enhanced sensory perception,51 a state of silent introspection, and feelings of wellbeing.51 52

Cannabinoids exert a negative effect on dopaminergic activity in the prefrontal cortex.52 For example, treatment with THC results in a change in regional cerebral blood flow in the rat. In particular, decreases have been measured to the hippocampus and the frontal and medial prefrontal cortices. However, changes have not been found in the ventral tegmentum, caudate nucleus, cerebellum, temporal cortex, parietal cortex, or occipital cortex.53 Likewise, as evidenced by functional nuclear magnetic resonance imaging, chronic marijuana users show decreased activity of the dorsolateral prefrontal cortex, an area highly associated with working memory.54 A decrease in prefrontal cortex metabolism has also been shown in rats chronically exposed to THC.55 It has been suggested that hypometabolism in prefrontal cortical regions may contribute significantly to the impaired cognitive processes associated with cannabinoid use.

Administration of the endogenous cannabinoid anandamide, which also binds to CB1 receptor, elicits similar effects to those produced by THC.56 Although some pharmacological differences exist between the plant derived THC and anandamide, systematic structure-activity relation studies have shown that the two compounds act at the CB1 receptor in a similar manner.56

The intense psychological experiences elicited by the activation of the endocannabinoid receptors are strikingly similar to the experience of the runner’s high. To compare, the mental changes that accompany long distance running include analgesia, sedation (post-exercise calm or glow), a reduction in anxiety, euphoria, and difficulties in estimating the passage of time.18 45 In addition, a recent study investigating analyser cognitive functioning during exercise has shown that prolonged running and cycling produces deficiencies in prefrontal dependent cognitive processes such as sustained attention and working memory.57 One possible explanation of these findings may be that the increased endocannabinoid release during exercise results in diminished metabolism in prefrontal regions while at the same time altering cognitive function and consciousness. Although such parallels are anecdotal and speculative, such comparisons have shed light on psychological and pharmacological phenomena in the past. As with the mental changes associated with long distance running, most of the psychological effects of the cannabinoids depend on set and setting.

Cannabinoids and motor behaviour

The highest concentration of CB1 receptors in the brain can be found in the basal ganglia, particularly in output nuclei, and the cerebellum, implicating the endocannabinoid system in the control of movement.29 62 Indeed, there is substantial evidence that cannabinoids affect motor behaviour.42 43 58

In a variety of species including humans, administration of plant derived endogenous and synthetic cannabinoids produces biphasic effects on locomotion.15 41 In larger doses, cannabinoid agonists produce well known and profound motor inhibition. Thus, as might be expected, cannabinoids have proven clinically useful in treating movement disorders such as tics, dyskinesia, tremors, and dystonia.58 59 These...
effects are reversed by administration of the selective CB₁ receptor antagonist SR141716A, providing evidence that cannabinoids mediate motor activity through the CB₁ receptor. In low doses, however, cannabinoids tend to produce hyperactivity.³⁴ ⁶³ ⁶⁶ For example, intracerebroventricular injection of low doses of anandamide increased locomotion, and systemic injections of low doses of anandamide stimulated behavioural activity in the open field.³⁶ ³⁸ Finally, CB₁ knockout mice are extremely hypoxic,⁶⁸ suggesting that one of the principal physiological roles of the endocannabinoid system may be the refinement of movements needed for coordinated locomotion.

Cannabinoids appear to modulate motor behaviour by altering the transmission of other transmitter systems in the basal ganglia. They appear to increase γ aminobutyric acid transmission (although this remains controversial), inhibit glutamate transmission, and inhibit the reuptake of dopamine.³³ ⁶² In addition, anandamide release in the dorsal striatum increases in freely moving rats, and it has been suggested that it acts as a striatal neurotransmitter in its own right⁷⁰ (for a thorough review, see Piomelli⁷¹).

It is worth noting that the basal ganglia have been implicated in the control of movements based on well learned motor behaviour. The more a motor skill is practiced and becomes automatic, the more the details of its execution come under the control of the basal ganglia.⁶⁶ Hence, we predict that higher level skills such as running, which are controlled to a higher degree by the basal ganglia than high level skills, such as basketball, hockey, or tennis, may more readily activate the endocannabinoid system.

Cannabinoids and addiction

There is also a close interaction between dopamine and the endocannabinoid system in structures that are implicated in the brain’s reward system. The dopamine D₁ and D₂ receptors are colocalised with the CB₁ receptor,⁵⁸ and it has been shown that the cannabinoids alter dopaminergic activity in the medial forebrain bundle.³⁴ Cannabinoids increase the firing rates of dopaminergic neurones in the ventral tegmentum, substantia nigra, and the medial forebrain bundle.⁵⁷ ⁶⁷ ⁶⁸ Withdrawal from cannabinoids, on the other hand, results in a decline in dopaminergic activity in the medial forebrain bundle.⁶⁹ Projections from the ventral tegmentum to the nucleus accumbens via the median forebrain bundle mediate the rewarding effects of most drugs of abuse, and the reinforcement properties for coordinated locomotor and cannabinoid effects appear to be mediated through this pathway.⁶⁷ Evidence now supports the hypothesis that both endocannabinoids and exogenous cannabinoids induce a selective release of dopamine in the shell of nucleus accumbens through CB₁ receptors.⁵³ This evidence also suggests that the activation of endogenous cannabinoids through exercise could account for exercise addiction. It also follows that pretreatment with selective dopamine or endocannabinoid receptor antagonists should block induction of an exercise induced high. These possibilities deserve scientific inquiry, although the ethics of such studies in humans would bring into question morale issues.

Long distance running has been described as “addictive.”⁷¹ This is not unlike the anecdotal “withdrawal” experiences usually described as a dysphoric state by many runners when forced by knee problems to switch to an alternative activity. Recent studies have resolved a long debated argument about the addictive properties of cannabinoids (for a thorough review, see Maldonado and Rodríguez de Fonseca).⁷² Rodents previously exposed chronically to high doses of THC and then treated with a CB₁ receptor antagonist such as SR141716A do, in fact, show signs of withdrawal syndrome.⁷² The somatic signs of withdrawal include wet dog shakes, front paw tremor, body tremor, hypolocomotion, ataxia, mastication, piloerection, excessive licking, scratching, and rubbing. It has been suggested that the failure to observe severe withdrawal symptoms in humans chronically exposed to marijuana may relate to the long half life of THC and its metabolites. This is compounded by the fact that THC and its psychoactive metabolites are extremely lipophilic. Thus, they are stored in fatty tissues and released slowly into the blood stream once abstinence is experienced. Collectively, these factors could counter acute withdrawal symptoms when chronic use of cannabis is terminated in both non-humans and humans.¹² ⁷³ ⁷⁴

Finally, increased corticotrophin releasing factor, and inhibition of mesolimbic dopamine activity is a common withdrawal symptom produced by many drugs of abuse.⁷⁴ Animals undergoing SR141716A induced cannabinoid withdrawal show increased corticotrophin releasing factor release and enhanced Fos activity in the central amygdala.⁷⁵ It has been hypothesised⁷⁶ that this change in limbic system corticotrophin releasing factor function could be responsible for the increased feelings of anxiety and depression that often accompanies cannabinoid withdrawal. This, along with the reduction in spontaneous firing of DA neurones in the ventral tegmentum during cannabinoid abstinence,⁷⁷ is thought to be the likely physiological mechanism responsible for the dysphoria associated with cannabis withdrawal.⁷⁸ We do not suggest that the addictive aspects of exercise are identical with the addictive properties of exogenous cannabinoids, but that a similarity exists between the desire that some people have for exercise and the desire they may have for exogenous administrations of cannabinoids. The parallels between these results and the subjective experiences associated with exercise abstinence, as discussed previously, are considerable.

Peripheral effects

Activation of the endocannabinoid system may also participate in other adaptive responses to exercise. For instance, anandamide acts as a vasodilator and produces hypotension⁷⁹ ⁸⁰ and may thus facilitate blood flow during exercise. Although the distribution of CB₁ receptors in smooth muscle and endothelial cells suggests that the vasorelaxant effects of endocannabinoids are mediated through CB₁ receptors, recent experiments⁷⁹ have intimated a prominent role of vanilloid receptors in the vasodilatory effects of these endocannabinoids. Finally, cannabinoids affect the respiratory system. Although studies have reported bidirectional control of airway responsiveness, in general, endocannabinoids and exogenous cannabinoids act as bronchodilators.¹⁴ Consequently, a possible role for the endocannabinoid system could be to facilitate breathing during exercise.

CONCLUSIONS

To date, a sound neural mechanism for the well known beneficial effects of exercise on mental health has yet to be proposed. Recent findings show that exercise increases serum concentrations of endocannabinoids, a result suggestive of a new possible explanation for a number of these changes. Further research is necessary to characterise the precise nature of this endocannabinoid response to exercise, specifically the relative importance of factors such as the nature of the activity, exercise duration, exercise intensity, sex, and age. In addition, animal models can be used to identify the production and binding sites of endocannabinoids as well as their functional role in exercise.

The cannabinoids produce psychological states that closely parallel several experiences described as being related to the runner’s high. Compared with the opioid analgesics, the analgesia produced by the endocannabinoid system is more consistent with exercise induced analgesia. Activation of the
endocannabinoid system also produces sedation, anxiolysis, a sense of wellbeing, reduced attentional capacity, impaired working memory ability, and difficulty in time estimation. This behavioural profile is similar to the psychological experiences reported by long distance runners. Considerable research is needed to clarify to what extent the endocannabinoid system might be responsible for the exercise induced changes in mental status. Nevertheless, a significant upregulation of serum concentrations of endocannabinoids has recently been reported in endurance athletes, and studies are underway to explore this further in laboratory animals. The close interaction of endocannabinoids with dopamine shows that they have a function in the brain’s reward system and therefore possibly addiction. The endocannabinoid system is also implicated in the control of motor activity mediated through the basal ganglia, and central activation of anandamide in freely moving rats has been demonstrated. Finally, the endocannabinoid system mediates peripheral effects such as vasodilation and bronchodilation that may play a contributory role in the body’s response to exercise. This article is intended to provide an overview of the emerging field of the endocannabinoid-exercise interaction. The list of topics was necessarily selective, but it is offered in the hope that researchers of diverse backgrounds will use the review to conduct empirical tests of its premises. We suggest that the “endocannabinoid hypothesis” is a feasible alternative to the endorphin hypothesis and should be subjected to further empirical tests.

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Reactivity to exercise can be enhanced by the activation of endocannabinoids. The presence of endocannabinoids has been demonstrated in various tissues, including the brain, heart, liver, and muscle. These molecules are involved in the regulation of a wide range of physiological processes, including pain perception, mood, and memory. The discovery of cannabinoid receptors and their associated signaling pathways has opened up new avenues for research and potential therapeutic applications.

**Conclusions:** The findings of this study suggest that endocannabinoids play a significant role in the reactivity to exercise. The activation of these endocannabinoids can enhance the body's physiological response to exercise, potentially improving performance and recovery. Further research is needed to fully understand the mechanisms involved and to explore the potential benefits of incorporating endocannabinoids in exercise regimens.

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