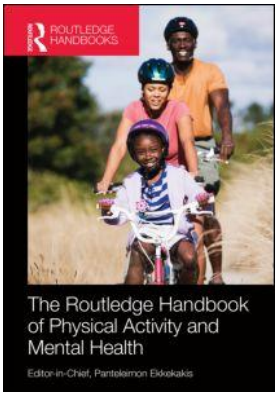

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PHYSICAL ACTIVITY AND REWARD

The role of endogenous opioids

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In humans, regular physical activity has been associated with a wide range of positive mental health outcomes in various affect-related domains beyond well-established effects on specific aspects of cognition (Hillman, Erickson, & Kramer, 2008). These include reduced symptoms of depression and anxiety (Byrne & Byrne, 1993; De Moor, Boomsma, Stubbe, Willemsen, & de Geus, 2008; Herring, O'Connor, & Dishman, 2010; Herring, Puetz, O'Connor, & Dishman, 2012; Krogh, Nordentoft, Sterne, & Lawlor, 2011; Mead, Morley, Campbell, Greig, McMurdo, & Lawlor, 2009; Morgan, 1985; Ströhle, 2009), lowered odds of developing depressive disorders or feelings of distress (Physical Activity Guidelines Advisory Committee, 2008), and elevated mood (Janal, Colt, Clark, & Glusman, 1984; Wildmann, Kruger, Schmole, Niemann, & Matthaei, 1986). Mood effects range from feelings of general well-being (Knechtle, 2004; Sher, 1996) and accomplishment (Conroy, Smith, & Felthous, 1982) to ecstatic affective states, referred to as "runner's high" (Partin, 1983; Wagemaker & Goldstein, 1980). Deprivation from regular exercise can be associated with mood disturbances, notably increased state anxiety, tension, depression, and confusion (Mondin et al., 1996). Beyond mood, there are indications that exercise training influences pain perception (Koltyn, 2000) and studies in humans (Droste, Greenlee, Schreck, & Roskamm, 1991; Janal et al., 1984; Koltyn, 2000) and animals (Shyu, Andersson, & Thoren, 1982) have demonstrated elevated pain detection thresholds as a consequence of exercise, although muscle pain during intense exercise may not depend on opiodergic influences on nociception (Cook, O'Connor, & Ray, 2000).

Despite considerable research efforts, up to now the neurobiological mechanisms underlying the benefits of being physically active remain poorly understood (Dishman et al., 2006) and also the circumstances (e.g., exercise duration and intensity, associated factors, etc.) causing positive aspects of exercise on mental health remain unclear (De Moor et al., 2008). While there is considerable progress in unveiling neurobiological mechanisms that may mediate cognitive improvement by exercise (Hillman et al., 2008), including neurotrophic factor release (Gomez-Pinilla, 2008; Vaynman & Gomez-Pinilla, 2005, 2006; Vaynman, Ying, & Gomez-Pinilla, 2004), neurogenesis/angiogenesis (van Praag, 2008), and neuroplasticity (Cotman & Berchtold, 2002), the central mechanisms mediating reward and pleasure in athletes remain far less well understood. Moreover, the understanding of the motivation to initiate and maintain a physically active lifestyle is still in its infancy, despite evidence that physical activity is strongly heritable (Bray et al., 2009; Stubbe et al., 2006).

There are different theories how exercise affects mood. Dietrich has proposed the "transient hypofrontality hypothesis" claiming an exercise-induced state of frontal hypofunction to account for effects of exercise on emotion and cognition (Dietrich, 2006). This theory has found support by ^{18}F-fluorodeoxyglucose (FDG) PET data of decreased prefrontal cortex metabolism during exercise (Tashiro et al., 2008), along with EEG changes in frontal brain areas (Schneider et al., 2009). However, the results of a recent systematic review and meta-analysis of 21 studies of exercise on brain hemodynamics measured by near-infrared spectroscopy (NIRS) in healthy adults are inconsistent with the "transient hypofrontality hypothesis" when it is applied to sub-maximal exercise (Rooks, Thom, McCully, & Dishman, 2010). The pattern of cerebral oxygenation, deoxygenation, and blood volume in the studies reviewed suggested responses opposite to the hypothesis. Only during highly intense, exhaustive exercise were cerebral oxygen values lowered. In contrast, moderate to hard sub-maximal exercise, the intensities that people select for their exercise and that elicit favorable moods, was accompanied by increases in cerebral oxygen and blood volume (Rooks et al., 2010). Related to this, Ekkekakis brought up the "dual-mode theory" (Ekkekakis, 2009), postulating that cognitive processing in prefrontal cortex shifts toward interoceptive processing in an exercise-intensity dependent manner. Other theories have focused on central neurotransmission, claiming effects of exercise on mood to be linked to biogenic amines (Chaouloff, 1989) and endorphinergic neurotransmission (Francis, 1983; Harber & Sutton, 1984).

This review will focus on the role of endorphins in exercise and how they affect pleasure and reward processing in athletes. The influential "endorphin hypothesis" (for a review, see Hoffmann, 1997) claims that endogenous opioid peptides are released in the human brain where they modulate affective processing and pain perception. However, after more than 30 years of human exercise research, the "endorphin hypothesis" is still under critical debate (Dishman, 1985; Dishman & O'Connor, 2009; Hinton & Taylor, 1986) as, for various reasons including methodological constraints, there has as yet been no direct proof in humans that exercise-induced mood changes are directly induced by endorphins in the central nervous system (CNS). Although opiate antagonists like Naloxone or Naltrexone have evoked positive associations of opioid actions and mood effects in most studies (Daniel, Martin, & Carter, 1992; Janal et al., 1984; Jarvekulg & Viru, 2002), although not unequivocally (Markoff, Ryan, & Young, 1982), the human findings generated so far were in essence indirect measures; for example, the demonstration of elevated beta-endorphin levels in plasma after exercise challenges does not inform about changes in central opioidergic neurotransmission because peripheral endorphins can only marginally reenter the brain through the blood–brain barrier (Dearman & Francis, 1983) and, thus, the relation between the peripheral and central opioidergic compartments remains unknown.

Only recently, PET ligand studies have been introduced as a more direct approach for studying opioidergic mechanisms in human exercise research (Boecker, Henriksen, et al., 2008; Boecker et al., 2010; Boecker, Sprenger, et al., 2008). Thereby, it has become possible to image opioidergic receptor binding within the entire human CNS *in vivo* and to assess binding changes related to exercise challenges. From a first application of this imaging method in athletes, evidence emerged to support that endogenous opioids are released in human brains after prolonged exercise (Boecker, Sprenger, et al., 2008). This technique may in future help resolve some of the unknown links between exercise, the central opioidergic compartment, and affective modulation in human athletes. Thus, future applications of behavioral and neuroimaging neuroscience to physical activity studies are necessary to elucidate, or eliminate, plausible opioidergic mechanisms, thereby advancing our understanding of the choice to be physically active and whether physical activity truly benefits mental health.

In the following, we will summarize the current state of research on the opioidergic system in exercise studies: first, we will describe the opioidergic system at the level of transmitters and receptors; second, we will summarize models of reward, hedonics, and motivation; third, we will summarize animal studies, and, finally, human studies examining the role of the central opioidergic system in mediating affective states through exercise.

The opioidergic system

Endogenous opioids have pharmacological actions similar to exogenous opiates like morphine. They act by binding to mu, kappa, or delta opioid receptors, and all three major representatives of the endogenous opioids carry variable affinities for mu, kappa, or delta opioid receptors. Due to their widespread distribution throughout the peripheral and central nervous system, endogenous opioids influence various bodily functions, from hedonics to pain regulation, but also cardiovascular, appetite, thirst, and temperature regulation (Akil et al., 1998; Evans, Hammond, & Fredrickson, 1988).

There are three major types of endogenous opioids: the beta-endorphins found primarily in the anterior and intermediate regions of the pituitary and released into the bloodstream, as well as the enkephalins and dynorphin, both distributed throughout many different CNS structures. More recently, another group of endogenous substances termed endomorphins (endomorphin-1 and endomorphin-2) have been discovered (Fichna, Janecka, Costentin, & Do Rego, 2007); through their particular affinity to the mu-receptor they can mimic their effects (Fichna et al., 2007). Whereas generation of euphoria has been linked to mu-receptor activation, dysphoric mood states have been associated with kappa-receptor activation (Bodnar, 2007).

In exercise research, studies on opioids have focused on beta-endorphins. They interact with mu- and delta-opioid receptors (Raynor et al., 1994). Peripherally, they are found in multiple organs like the eyes, the heart, the kidneys, the gastrointestinal tract, and the adrenal glands. Centrally, they are found in the spinal cord and in the brain (Imura & Nakai, 1981), the highest concentration being in the hypothalamus, but also in the limbic system, the periaqueductal gray (PAG), and the brainstem (Hegadoren, O'Donnell, Lanius, Coupland, & Lacaze-Masmonteil, 2009). The PAG is a key area of the descending anti-nociceptive pathway that mediates opioidergic anti-nociceptive effects (Sandkuhler, 1996). Neurons expressing the precursor protein proopiomelanocortin (POMC) are also found in the ventral tegmental area (VTA) and the nucleus accumbens (Leriche, Cote-Velez, & Mendez, 2007), whereby beta-endorphins are thought to modulate hedonics and appetitively motivated behaviors. Beta-endorphins produce hypoalgesia, respiratory depression, bradycardia, miosis, and hypothermia.

The enkephalins (leu-ENK and met-ENK) bind preferentially to delta-opioid receptors (Akil et al., 1998) and influence nociception, reward, and stress responses. Enkaphalins are thought to maintain normal affective tone through their interaction with delta receptors (Perrine, Sheikh, Nwaneshiudu, Schroeder, & Unterwald, 2008; Torregrossa et al., 2006) and ENK desensitization of delta opioid receptors in the ventral striatum, a critical neural circuit for affective modulation of endogenous opioids (Smith & Berridge, 2007), induces anxiety and depression-like effects. Furthermore, ENK influence stress, and nociception via the amygdala, the PAG, and the dorsal horn of the spinal cord (Akil et al., 1998; Jonsdottir, 2000a).

The distribution of dynorphin (DYN A, DYN B) generally overlaps with that of ENK but the behavioral functions are often opposite. DYN binds primarily to kappa-opioid receptors, thereby mediating stress-induced dysphoria (Land et al., 2008) and aversion via projections from the dorsal raphe nuclei to the nucleus accumbens (Land et al., 2009). Within the striatum, DYN is found particularly in medium spiny neurons that express the dopamine D-1 receptor subtype

(Jonsdottir, 2000b). DYN effects on the kappa-opioid receptor inhibit dopamine release in the VTA and nucleus accumbens (Mansour, Fox, Akil, & Watson, 1995; Nestler & Carlezon, 2006; Shippenberg & Rea, 1997).

Models of reward, hedonics, and motivation

It is important to consider that neurobiological theories of mechanisms mediating motivational and hedonic behavioral processes are not focused on the opioidergic system alone. Functional interactions exist between the opioidergic and the dopaminergic system and both transmitter systems are implicated in partly overlapping aspects of behavioral regulation. Beyond their involvement in central pain control (Bencherif et al., 2002; Casey et al., 2000; Zubieta, Heitzeg, et al., 2003; Zubieta et al., 2001), endogenous opioids mediate affective (Carr, 1984; Kehoe & Boylan, 1994; Zubieta, Ketter, et al., 2003), motivational (Carr, 1984), and stress responses (Drolet et al., 2001). Dopamine, on the other hand, is the principal neurotransmitter for central motor control (Brooks, 2001), but is also involved in cognitive processing (Kaasinen & Rinne, 2002; Pillon, Czernecki, & Dubois, 2003; Rinne et al., 2000), motivation (Volkow et al., 2002), and reward-associated behavior (Hakyemez, Dagher, Smith, & Zald, 2008; Martin-Soelch et al., 2001; Pappata et al., 2002; Zald et al., 2004). Finally, both, the opioidergic (DiChiara, Acquas, & Tanda, 1996; Herz, 1996, 1997) and dopaminergic (Volkow, Fowler, & Wang, 2004; Volkow et al., 2003) systems are "key players" in the development and maintenance of addictive behavior.

Dopamine and opioid receptors are G-protein coupled metabotropic receptors. Anatomically, there is widespread overlap in the expression of the opioidergic and the dopaminergic system in many parts of the CNS, which have been characterized best in the basal ganglia and midbrain circuits. In the rat VTA, approximately 50–60% of enkephalin-immunoreactive terminals that have synaptic contacts show association with tyrosine hydroxylase (TH) -labeled dendrites (Sesack & Pickel, 1992). Fluorescent micrographs suggest that high-affinity opiate binding sites are located primarily on dopaminergic presynaptic terminals (Stefano, Zukin, & Kream, 1982); however, enkephalin immunoreactivity has also been described in small unmyelinated axons (Garzon & Pickel, 2002). Dopaminergic neurons in the substantia nigra (SN) express kappa-opioid receptors on the terminal regions of their perikaria (Yamada, Groshan, Phung, Hisamitsu, & Richelson, 1997) and mu-opioid receptors are expressed in the retrorubral field, the substantia nigra (SN), and the VTA. The opioidergic receptor expression in these nuclei is region specific (German, Speciale, Manaye, & Sadeq, 1993). For instance, whereas the ventral pars compacta of the SN, which contains numerous DA neurons, has prominent mu-opioid receptor binding, lower receptor densities were observed in rostral portions of the VTA (German et al., 1993).

Hence, in order to understand the relative roles of motivational and hedonic processes in the antecedents and consequences of exercise, one must consider mutual interactions between opioid peptides and dopamine. The mesolimbic dopamine system has been associated with mediating behavioral responses to natural rewards, including food intake, reproductive behavior, play, etc. (Berridge & Robinson, 1998; Lutter & Nestler, 2009; Robbins & Everitt, 1996; Wise, 2004). Although dopamine was traditionally conceived as mediating hedonic aspects of reward (Koob & Le Moal, 1997; Wise, 2008), there is now accumulating evidence that it is more involved in motivational aspects of reward, rather than "pleasure" per se (Berridge & Robinson, 1998; Flagel et al., 2011; Smith & Berridge, 2007).

There are two important models related to dopamine-opioid interactions and their implications for addictive behavior: the "incentive salience hypothesis" which emphasizes the importance of dopamine as a motivator, driving the "wanting" aspect triggered by conditioned stimuli.

According to the "incentive salience hypothesis," the "liking" or "pleasure" associated with reward is mediated by other hedonic-based systems like GABA and opioid peptides (Smith & Berridge, 2007). On the other hand, models centered on the role of hedonics rather than motivational processes, such as the "hedonic allostasis theory," conceptualize addictive behaviors as a response to hypoactivity in dopamine systems (Koob & Le Moal, 1997). This hypo-dopaminergic state is postulated to induce compensatory behavioral activation (e.g., sensation-seeking, drug-seeking, compulsive exercise, etc.) to restore normal hedonic tone. Compulsive exercise or "addiction" to exercise thus would depend on correcting a dysphoric state caused by low dopaminergic (and presumably also opioidergic) tone. This is in contrast to the "incentive salience hypothesis," which predicts that higher dopaminergic transmission would lead to appetitively motivated behaviors such as exercise.

The opioid system in animal exercise studies

Elevated serum opioid activity has been demonstrated after exercise challenges in animals (Debruille et al., 1999), but it is unique to animal work that opioid receptor distributions can be directly studied in the CNS. Early ligand-binding studies showed altered opiate receptor occupancy in the rat brain following acute exercise (Pert & Bowie, 1979; Wardlaw & Frantz, 1980). However, subsequent studies produced conflicting results: chronic treadmill running did not alter basal levels of brain opioid peptides (Houghten, Pratt, Young, Brown, & Spann, 1986); upon acute exercise challenges, either beta-endorphin levels were higher in the nucleus accumbens after 2 hours of forced treadmill running (Blake, Stein, & Vomachka, 1984), or exercise was associated with lower levels of endorphins (Sforzo, Seeger, Pert, Pert, & Dotson, 1986), as evidenced by increased [^{3}H]diprenorphine binding in target brain regions after 2 hours of forced swimming. As those studies used forced exercise paradigms – which may be problematic as stress hormones can cause opioid release (Nikolarakis, Pfeiffer, Stalla, & Herz, 1987) – and did not measure behavioral responses representative of euphoria, hypoalgesia, or anxiolysis, these results neither supported nor refuted the "endorphin hypothesis" of exercise on mood and/or pain. It has been shown, however, that voluntary exercise increases DYN-converting enzyme activity in rat CSF, thereby converting DYN to leu-enkephalin (Persson et al., 1993). DYN is also released in the paraventricular nucleus (PVN), together with leu-ENK in the caudate-putamen after high-intensity aerobic exercise (Chen, Zhao, Yue, & Wang, 2007).

The role of the dopaminergic system will be further elucidated in other chapters of this book. It should be briefly noted here that treadmill running also increases dopamine release (Meeusen, Piacentini, & De Meirleir, 2001). Exercise also increases dopamine turnover (Hattori, Naoi, & Nishino, 1994) and chronically up-regulates D2 receptors (MacRae, Spirduso, Walters, Farrar, & Wilcox, 1987) in the striatum of rats. In contrast to acute effects of treadmill running, striatal DA activity has been reduced after chronic exposure to wheel running in highly fit rats (Swallow et al., 2008), whereas gene expression for D2 receptors in the nucleus accumbens was unchanged (Knab, Bowen, Hamilton, Gulledge, & Lightfoot, 2009) or decreased after chronic wheel running (Greenwood et al., 2011).

Another approach to determine whether an experimental challenge activates a specific endogenous neurotransmitter is to test whether repeated exposure to that manipulation produces tolerance to drugs that mimic the neurotransmitter. For the opioidergic system, the anti-nociceptive effects of exogenous opiates are attenuated by exercise. This is referred to as "cross-tolerance" (Mathes & Kanarek, 2001) and it was shown that exercise produces a cross-tolerance to the analgesic effects of morphine (Smith & Lyle, 2006). Similar effects can also be elicited directly by local morphine administration into the PAG (Mathes & Kanarek, 2006). Naloxone-

precipitated withdrawal is also exaggerated following chronic wheel running (Kanarek, D'Anci, Jurdak, & Mathes, 2009).

Exercise genetics have become another line of investigation, as there is evidence that physical activity impacts gene expression of beta-endorphin, ENK, and DYN (Jonsdottir, Hoffmann, & Thoren, 1997; Mathe, Bjornebekk, & Brene, 2006). Running increases DYN mRNA levels in the caudate putamen of rats bred for running and drug preference (Werme, Thoren, Olson, & Brene, 2000). Additionally, the effect is blocked by the opioid receptor antagonist naloxone, indicating not only up-regulation of mRNA, but also mu-receptor activation (Werme et al., 2000). As opioid modulation of brain dopamine is a core feature in models of motivated behavior and addiction (see above), it is interesting to notice that the transcription factor DeltaFosB is overexpressed in the nucleus accumbens of rats exhibiting spontaneous wheel running (Werme et al., 2002). DeltaFosB could facilitate wheel running by inhibiting the release by GABA neurons of co-localized dynorphin, which otherwise binds with kappa-opioid receptors to inhibit DA release in the VTA or accumbens (Werme et al., 2002). In short, it is plausible that central opioids modulate dopamine and/or other neurotransmitter systems that control metabolic or hedonic drives regulating physical activity (Nestler & Carlezon, 2006; Werme et al., 2002).

Human plasma beta-endorphin studies in exercise

Mood and affect can be investigated most informatively in humans, as the use of affective self-evaluations and neuropsychological scales for mood and hedonics provide a major advantage compared to animal studies. Indeed, a general problem in animal research is that operational measures of hedonics are difficult to validate (Holmes, 2003). Up to now, human research has focused on endorphin levels in the peripheral compartment, as direct investigations of the CNS in athletes have been prohibited due to ethical constraints.

During vigorous exercise, beta-endorphin release from the pituitary is usually accompanied by increases in ACTH, which is derived along with beta-endorphin and melanocortin from the common precursor POMC. Hence, peripheral levels of beta-endorphins during and shortly after acute exercise may be viewed as an indication of the stress response to the exercise. Opioid peptides are reliably elevated in the plasma of humans during intense exercise (Carr et al., 1981; Farrell, Gates, Maksud, & Morgan, 1982; Gambert et al., 1981), but they show a considerable intra- (Sheps, Koch, Bragdon, Ballenger, & McMurray, 1988) and inter-individual (Farrell et al., 1982; Goldfarb & Jamurtas, 1997) variability. According to a recent review (Boecker et al., 2010), a large majority (59 of 65) of studies (from 1982 to 2008) showed significant increases of peripheral beta-endorphin concentrations, despite highly heterogeneous exercise challenges. It remains unclear whether plasma beta-endorphins, and their precursor molecule POMC, show a clear dose-gradient response to exercise (Goldfarb & Jamurtas, 1997; Harbach & Hempelmann, 2005; Nybo & Secher, 2004). Although several studies (Bullen et al., 1984; de Vries, Bernards, de Rooij, & Koppeschaar, 2000; Farrell, Kjaer, Bach, & Galbo, 1987; Goldfarb, Hatfield, Armstrong, & Potts, 1990; Goldfarb, Hatfield, Potts, & Armstrong, 1991; Goldfarb et al., 1998; McMurray, Forsythe, Mar, & Hardy, 1987; McMurray, Hardy, Roberts, Forsythe, & Mar, 1989; Rahkila, Hakala, Alen, Salminen, & Laatikainen, 1988; Viru & Tendzegolskis, 1995; Viswanathan, Vandijk, Graham, Bonen, & George, 1987) have demonstrated that strenuous exercise regimes are associated with higher magnitudes of peripheral endorphins than low-intensity exercise challenges, research suggests that these peripheral changes are not reflective of beta-endorphin concentrations in the brain (Boecker et al., 2010). After strenuous exercise, raised beta-endorphins in plasma tend to wash out slowly over a time-span of several hours and this wash-out was slower during recovery from a marathon race than after an exhausting incremental graded treadmill

exercise (Heitkamp, Schmid, & Scheib, 1993). In humans, protracted miosis up to 6 hours has been demonstrated after more than 30 minutes of exercise, an effect that is very likely due to opioidergic mechanisms, as it can be blocked by naloxone eye drops (Allen, Thierman, & Hamilton, 1983). This review (Boecker et al., 2010) revealed that the endorphin literature up to now has not been able to establish consistent links between (peripheral) opioid peptides in plasma and (central) behavioral effects on mood and pain perception. The association between peripheral beta-endorphin values and mood is highly inconsistent, with only two out of seven reviewed studies showing a positive relationship between both factors (Harte, Eifert, & Smith, 1995; Janal et al., 1984). Hence, levels of opioid peptides in plasma following exercise challenges do not allow extrapolating upon central opioidergic transmitters or upon central transmitter actions at the opioid receptor level. It has been claimed, therefore, that the brain during exercise is affected by opioids other than those derived from POMC in the pituitary (Fallon & Leslie, 1986), whereas peripheral opioid peptides help regulate physiological responses that support energy expenditure and modulate nociception during exercise (Dishman, 1985; Nybo & Secher, 2004; Rossier et al., 1977).

Human opioid receptor PET studies in exercise

Recent developments in functional neuroimaging have provided alternative and promising approaches for unveiling opioidergic effects in human exercise research: the applicability of PET with suitable opioidergic tracers allows non-invasive *in vivo* monitoring of both acute opioidergic transmitter trafficking and chronic changes of opioid receptor expression in human athletes. Available are PET tracers with either non-specific ([^{11}C]diprenorphine, [^{18}F]diprenorphine, non-selective antagonist) or subtype-specific binding properties ([^{11}C]carfentanil, mu-opioid receptor agonist; [^{18}F]fluoro-cyclofoxy, mu/kappa-opioid receptor antagonist). As studies in humans have the advantage, as compared to animals, that mood effects can be captured using appropriate rating scales, acute opioid trafficking and long-term opioid receptor binding changes associated with exercise can be linked to individual affective states. In the following, we will summarize the findings of a first published opioid PET ligand study using endurance exercise training as experimental challenge (Boecker, Sprenger, et al., 2008).

The tracer 6-O-(2-[^{18}F]fluoroethyl)-6-O-desmethyldiprenorphine ([^{18}F]FDPN), which has similar selectivity to mu, delta, and kappa opioid receptors (Wester et al., 2000), was applied in 10 trained male athletes (mean age 36.9 years ± 2.6) to test the effect of 2 hours' endurance running as exercise challenge. Each participant received two PET scans on separate days in random order: rest (no sport 24 hours prior to PET), post-exercise (directly after 2 hours of running). During exercise, the average pace was of 11.0 ± 2.3 km/h, the average heart rate 144±7 min^{-1}. The euphoria ratings on visual analog scales increased significantly from 37.6 ± 19.6/100 (prior to exercise) to 73.3 ± 13.2/100. This was associated with a significant reduction of [^{18}F]FDPN binding after exercise, confirming the study hypothesis of elevated endogenous opioid tone induced by running. For the first time it was possible to study the localization of these ligand binding changes after acute exercise bouts *in vivo*. Interestingly, the most preponderant effects were encountered in prefrontal/orbitofrontal cortices, and also extensively in limbic structures (anterior cingulate cortex, insula).

The opioid PET data are indicative of elevated endogenous opioid levels post-exercise in areas of the brain (anterior cingulate cortex, and insula/parainsular cortex) implicated in affective processing (Dalgleish, 2004). More specifically, the location of these effects is well in accord with current theories of opioid-generated pleasure (Kringelbach & Berridge, 2010).

Summary

How exercise influences mood states is an important experimental question; however, after more than 30 years of research, the role of opioids in exercise-related hedonics is still unclear. While exogenously administered opiates induce euphoric states, it is rather unusual that athletes have comparably strong mood changes simply by engaging in physical activity, as this would not make "biological sense" in the absence of severe physical stress or trauma. Although a great deal of research data argue for the participation of endogenous opioids in mood regulation during and after exercise, most of the evidence is "indirect," and up to now causal effects of opioids on mood processing remain to be determined.

Animal studies show increased levels of endorphins or altered enkephalin receptor binding in the brain after acute exercise, but emotional effects are difficult to study in animals. In humans, the current state of knowledge is also still in a premature stage: studies using opioid receptor blocking approaches have revealed equivocal results regarding exercise effects on mood. The relation between endorphins in the peripheral blood and the CNS is still unknown, so it is questionable whether conventional blood-based methods yield relevant information on central neurotransmitter effects. It is expected for the future that ligand PET applications in athletes may help uncover some of the hitherto unknown links between opioidergic neurotransmission and psychophysiological effects in exercise. The authors of this chapter, therefore, make the claim that future studies should synergize human brain imaging with behavioral neuroscience approaches based on animal models.

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