

# Advocating neuroimaging studies of transmitter release in human physical exercise challenges studies

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**Abstract:** This perspective attempts to outline the emerging role of positron emission tomography (PET) ligand activation studies in human exercise research. By focusing on the endorphinergic system and its acclaimed role for exercise-induced antinociception and mood enhancement, we like to emphasize the unique potential of ligand PET applied to human athletes for uncovering the neurochemistry of exercise-induced psychophysiological phenomena. Compared with conventional approaches, in particular quantification of plasma beta-endorphin levels under exercise challenges, which are reviewed in this article, studying opioidergic effects directly in the central nervous system (CNS) with PET and relating opioidergic binding changes to neuropsychological assessments, provides a more refined and promising experimental strategy. Although a vast literature dating back to the 1980s of the last century has been able to reproducibly demonstrate peripheral increases of beta-endorphin levels after various exercise challenges, so far, these studies have failed to establish robust links between peripheral beta-endorphin levels and centrally mediated behavioral effects, ie, modulation of mood and/or pain perception. As the quantitative relation between endorphins in the peripheral blood and the CNS remains unknown, the question arises, to what extent conventional blood-based methods can inform researchers about central neurotransmitter effects. As previous studies using receptor blocking approaches have also revealed equivocal results regarding exercise effects on pain and mood processing, it is expected that PET and other functional neuroimaging applications in athletes may in future help uncover some of the hitherto unknown links between neurotransmission and psychophysiological effects related to physical exercise.

**Keywords:** positron emission tomography, beta-endorphins, opioids

## Introduction

Regular physical exercise is associated with a wide spectrum of psychophysical effects, including anxiolysis,<sup>1</sup> stress reduction,<sup>2</sup> mood elevation,<sup>1,3-5</sup> and altered pain perception.<sup>3</sup> The underlying neurotransmitter effects (eg, dopaminergic, opioidergic, endocannabinoid, and serotonergic) in the central nervous system (CNS) and their specific roles for induction and maintenance of distinct psychophysiological phenomena are subject to both nonhuman and human exercise research. Although animal studies allow direct quantitative and regional assessments of neurotransmitter trafficking in the CNS via invasive microdialysis measurements in exercising animals,<sup>6</sup> or postmortem autoradiography of receptor binding changes after exercise,<sup>7</sup> until recently, human studies examining neuro-humeral effects of exercise have been derived exclusively from indirect peripheral neurotransmitter levels in plasma and receptor blockade studies (discussed later).

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The central endorphinergic system, which is the focus of this article, has been linked to exercise-induced mood changes<sup>1,3,4,8-11</sup> and antinociceptive effects referred to as stress-induced analgesia.<sup>3,9,10</sup> The endorphinergic system can be studied in human athletes via measurements of peripheral beta-endorphin material, receptor blocking studies, or, more directly using positron emission tomography (PET) ligand displacement approaches (discussed later). This perspective, by contrasting the data derived from peripheral beta-endorphin measurements with initial PET studies in athletes, aims at highlighting the unique and unprecedented potential of PET ligand activation studies for exploring central neurotransmission related to physical exercise.

## Measurements of peripheral beta-endorphin levels in exercise studies

Endogenous opioid peptides (endorphins, enkephalins, and dynorphins) interact with  $\mu$ ,  $\kappa$ , and  $\delta$  opioid receptors located in the CNS and the peripheral nervous system. During vigorous exercise, beta-endorphins are released from the pituitary gland into the blood, although with considerable intra-individual variability<sup>12</sup> and inter-individual variability.<sup>13,14</sup> Table 1 summarizes published data on this topic, as compiled from a PubMed search: “Exercise and Human and Plasma and Endorphin”, which revealed 185 hits spanning from 1982 to 2008. We excluded work examining the effects of resistance training on beta-endorphin plasma levels,<sup>15</sup> and we also excluded studies conducted in patient populations. Our inquiry resulted in 65 studies covering a wide range of physical exercise challenges from low to maximal intensity. Although we can make no claim of completeness regarding included studies, the summarized papers indicate that a high percentage of exercise-induced beta-endorphin plasma elevations. As can be seen from Table 1, 59 of 65 papers identified significant increases of peripheral endorphin values, despite highly heterogeneous exercise challenges. Studies applying different exercise intensity levels have shown a positive relationship between the intensity of exercise challenges and the magnitude of peripheral endorphin increases in plasma.<sup>16-27</sup>

## Link between peripheral beta-endorphin levels and mood and pain assessments

Despite these highly reproducible increases of beta-endorphins in peripheral blood after exercise, as shown in Table 1, the correlation of peripheral beta-endorphin values with behavioral measures of altered mood or pain processing has yielded

equivocal results.<sup>28</sup> This may be linked to the fact that most of these large molecules can only bypass the blood-brain barrier to a very minor extent.<sup>29</sup> Table 2 summarizes those studies that have correlated peripheral endorphin values after exercise challenges with changes in mood states, whereas Table 3 summarizes those studies that have correlated peripheral endorphin values after exercise challenges with pain scores. It can be seen from Table 2 that the association between peripheral beta-endorphin values and mood is indeed highly inconsistent, with only two out of 7 studies showing a positive relationship between both factors.<sup>3,30</sup> Only 3 studies, we are aware of, have tested the relationship between exercise-induced peripheral beta-endorphin values and changes in pain ratings (Table 3). All of them have demonstrated exercise-induced hypoalgesia; however, only two of these identified a positive relationship between endorphins and hypoalgesia.<sup>3,31</sup>

Based on the available limited evidence, at present no clear relationship between peripheral endorphin levels and modulation of mood/pain processing can be established, thus arguing against a linear relationship between the peripheral and the central opioidergic compartments. Moreover, these negative findings are also at odds with the acclaimed role of exercise in promoting antinociception and mood enhancement. Therefore, we conclude that peripheral measurements of endorphins provide only limited information about central opioidergic mechanisms underlying psychophysiological effects. This also seems to apply to receptor blocking studies, which are not summarized here in detail, but which have also revealed equivocal results, ie, either negative<sup>32-35</sup> or positive blocking effects in the pain domain.<sup>3,36</sup> On the other hand, several studies have reported positive blocking effects in the mood domain,<sup>3,37,38</sup> thus supporting the hypothesis of central opioidergic effects mediating mood enhancement. Alternatively, quantification of neurotransmitter levels in the cerebrospinal fluid compartment of the CNS<sup>39</sup> seems to provide a more direct approach, and may yield more distinct information than plasma values. Yet, given the invasiveness of repetitive spinal fluid taps, this experimental approach has to be refuted for ethical reasons in humans. Moreover, any quantitative analysis of neurotransmitters in spinal fluid or plasma will not inform researchers about the site of neurotransmitter actions in the CNS and, therefore, will not be able to establish precise correlations with neurobehavioral measures.

## PET ligand activation of the opioidergic system

PET studies allow noninvasively quantifying receptor binding of PET ligands within the entire CNS and, more recently,

**Table 1** Papers reporting peripheral beta-endorphin values in exercise challenges

Publication	N/sex	Age	Fitness state	Exercise type	Duration/distance	Intensity level	Significance (endorphine increase)
48	9/M	27.6 ± 1.6	Highly fit	Treadmill	30 min	80% VO <sub>2</sub> max	<i>P</i> < 0.05
49	15/M	28.5 ± 9.5	Unfit	Cycle ergometer	60 min	60% VO <sub>2</sub> max 80% VO <sub>2</sub> max	Significant
50	10/M	32.3 ± 10.6	Fit	Treadmill	30 s	424.8 ± 41.9 W	<i>P</i> < 0.001
16	7/F	24.6 ± 4.2	Fit	Cycle ergometer	60 min	20 min 50% 20 min 70% 10 min 80–85% VO <sub>2</sub> max	NS NS <i>P</i> < 0.05
51	24/M	12.85 ± 0.054	Fit	Cycle ergometer	15 min	90% VO <sub>2</sub> max	<i>P</i> < 0.01
	16/F	10.87 ± 0.47					
52	13/M	18.6 ± 0.7	Highly fit	Swimming (100 m freestyle)	61.47 ± 1.98 s	Competition condition	<i>P</i> < 0.01
53	20/M	34.4 (27–42)	Highly fit	Outdoor running	30 min	“Easy run” Maximal pace	<i>P</i> < 0.067 (NS) <i>P</i> < 0.008
	6/F	31.2 (28–41)					
54	11/M	20–24	Fit to highly fit	Treadmill	–	Graded intensity to exhaustion	<i>P</i> < 0.05
	8/M		Unfit				
55	11/M	–	–	Cycle ergometer	–	Graded intensity to exhaustion	<i>P</i> < 0.05
56	14/M	26.7 ± 3.2	Fit	Cycle ergometer	60 min	112 ± 16 W (<70% max HR)	NS
17	8/M	21.9 ± 2.4	–	Cycle ergometer	40 min	40% VO <sub>2</sub> max 60% VO <sub>2</sub> max 80% VO <sub>2</sub> max 100% VO <sub>2</sub> max 10 min each to exhaustion	NS NS NS <i>P</i> < 0.01
57	18/M	20.8 ± 0.2	Highly fit	Treadmill	30 min	Anaerobic threshold	NS
58	19/M	21.9 ± 1.9	Unfit	Cycle ergometer	32 min	Graded intensity to exhaustion	<i>P</i> < 0.05
59	10/M	33 (20–46)	Fit	Cycle ergometer	–	Graded intensity to exhaustion	<i>P</i> < 0.0001
60	8/M	26.8 ± 8.6	Unfit	Treadmill	20 min	80% max HR	NS
61	5/M	–	Unfit	Treadmill	–	Graded intensity to exhaustion	<i>P</i> < 0.05
13	5/M	30.0 ± 8.3	Highly fit	Treadmill	30 min	60% VO <sub>2</sub> max 80% VO <sub>2</sub> max	<i>P</i> < 0.05 NS
	1/F						
18	7/M	23.1 ± 2.5	Fit	Treadmill	12 min	7 min 60% VO <sub>2</sub> max	NS
	7/M	23.0 ± 3.5	Unfit			3 min 100% VO <sub>2</sub> max	<i>P</i> < 0.05
62	10/M	26.3 ± 5.4	Fit	Cycle ergometer	120 min	2 min 110% VO <sub>2</sub> max 65% VO <sub>2</sub> max	<i>P</i> < 0.05 <i>P</i> < 0.05
63	21/F	14	Fit	Step test	3–6 min	To 66% VO <sub>2</sub> max	<i>P</i> < 0.05
64	8/M	45.9 ± 8.7	Highly fit	Outdoor running	21–42 km	Race conditions	<i>P</i> < 0.001
	7/F	46.3 ± 5.3					
65	9/M	20–28	Unfit	Cycle ergometer	–	Graded intensity to exhaustion	<i>P</i> < 0.05
19	12/M	26.5 ± 1.3 (21.37)	–	Cycle ergometer	30 min	60% VO <sub>2</sub> max 70% VO <sub>2</sub> max 80% VO <sub>2</sub> max	NS <i>P</i> < 0.05 <i>P</i> < 0.05
20	6/M	28.0 ± 2.2	Fit	Cycle ergometer	30 min	60% VO <sub>2</sub> max	NS
	6/M	25.0 ± 1.4	Unfit			70% VO <sub>2</sub> max 80% VO <sub>2</sub> max	<i>P</i> < 0.05 <i>P</i> < 0.02
21	12/M + F	26.4/26.8	–	Cycle ergometer	2 × 25 min	60% VO <sub>2</sub> max 80% VO <sub>2</sub> max	NS <i>P</i> < 0.05

(Continued)

Table 1 (Continued)

Publication	N/sex	Age	Fitness state	Exercise type	Duration/ distance	Intensity level	Significance (endorphine increase)
66	14/M	25.6 ± 2.1	Fit	Outdoor running + upstairs running (8 floors)	3 km	Individual maximal pace	P < 0.05
30	11/M	31.3	Highly fit	Outdoor running	60 min/15 km	Fast training pace	P < 0.0001
31	50/F	–	–	Cycle ergometer	20 min	Moderate intensity	P < 0.001
67	9/M	21.1 ± 2.52	Unfit	Cycle ergometer	–	Graded intensity to exhaustion	P < 0.001
68	7/M	66.0 ± 5.85					
68	16/M	38	Highly fit	Cycle ergometer	–	Graded intensity to exhaustion	P < 0.001
				Outdoor running	42 km	Race condition (83% VO <sub>2</sub> max)	P < 0.001
69	14/F	–	Highly fit	Outdoor running	3:22 h/42 km	Race condition	Significant
				Treadmill running	–	To exhaustion	Significant
70	23/F	21.7 ± 1.9	Unfit	Treadmill	30 min	Graded intensity to exhaustion	P < 0.05
71	5/M	22.6 ± 1.3	Highly fit	Cycle ergometer	60 min	70% VO <sub>2</sub> max	P < 0.05
72	18/F	20–23	Unfit	Treadmill	60 min	60% VO <sub>2</sub> max 70% VO <sub>2</sub> max 80% VO <sub>2</sub> max 20 min each	P < 0.01
3	12/M	38.3	Highly fit	Outdoor running	43.9 min/ 6.3 miles	85% VO <sub>2</sub> max	P < 0.01
73	6/M	26.5 ± 4.5	Fit	Cycle ergometer	120 min	50% VO <sub>2</sub> max	P < 0.05
74	10/M	23.9 ± 3.8	–	Cycle ergometer	<1–4 min	115% VO <sub>2</sub> max 175% VO <sub>2</sub> max 230% VO <sub>2</sub> max 318% VO <sub>2</sub> max	P < 0.05 NS NS NS
75	8/M + F	26.5 ± 5.0	Unfit	Treadmill	–	Maximal intensity	P < 0.05
	10/M + F	23.1 ± 4.1					
	7/M + F	21.9 ± 3.1					
76	6/M	22 ± 2	Fit	Cycle ergometer	7–8 min	3 min 90% VO <sub>2</sub> max 3–4 min 100% VO <sub>2</sub> max	P < 0.05 P < 0.05
77	8/M, 5/F	31.5 ± 30.4	Fit	Treadmill	30 min	80% max HR	NS
	5/M, 5/F	29.6 ± 28.8	Unfit				
78	5/M	22 ± 2	Fit	Cycle ergometer	60 min	60% VO <sub>2</sub> max	NS
	5/M	22 ± 2	Fit	Treadmill	60 min	0% VO <sub>2</sub> max	NS
22	20/M	26 ± 1	Highly fit	Cycle ergometer	120 min	120 min 65% VO <sub>2</sub> max	NS
					120 min + 1 min sprint	120 min 65% VO <sub>2</sub> max + sprints a 120% VO <sub>2</sub> max	P < 0.001 (after sprints)
79	6/M	33.5 ± 8.6	Fit	Cycle ergometer	–	Graded intensity to exhaustion	P < 0.05
23	10/M	24.5 ± 4.8	Unfit	Cycle ergometer	3 × 20 min	40% VO <sub>2</sub> max 60% VO <sub>2</sub> max 80% VO <sub>2</sub> max 20 min each	NS NS P < 0.05
80	7/F	23.4 ± 1.4	Fit	Treadmill	2 × 60 min	80% VO <sub>2</sub> max	P < 0.05

(Continued)

Table I (Continued)

Publication	N/sex	Age	Fitness state	Exercise type	Duration/distance	Intensity level	Significance (endorphine increase)
24	5/M + 5/F	26.9 ± 6.7	Fit	Cycle ergometer	3 × 20 min	40% VO <sub>2</sub> max	NS
	5/M + 5/F	21.0 ± 2.9	Fit			60% VO <sub>2</sub> max	NS
						80% VO <sub>2</sub> max	P < 0.05
						20 min each	P < 0.05
81	14/M	18–25	Mixed	Cycle ergometer	4 × 30 min	75% VO <sub>2</sub> max	P < 0.003
82	10/F	18–21	Highly fit	Cycle ergometer	–	Graded intensity to exhaustion	P < 0.001
83	8/M	22.1 ± 2.7	Fit	Cycle ergometer	90 min	65% watt max	P < 0.05
84	11/M	34 ± 2.3	Highly fit	Ski race	75.7 km	Race conditions	P < 0.001
	6/M	38.1 ± 4.3	Fit				
85	17/M	39.8 ± 10.3	Mixed	Treadmill	15 min	Graded intensity to exhaustion	P < 0.01
86	9/M	–	Highly fit	Outdoor running	70–80 min/22 km	Race condition	P < 0.05
36	17/M	26 (22–32)	Fit	Outdoor running	12 min	Maximal pace	P < 0.05
87	4/M	45	Highly fit	Outdoor running	7 d 23 h/1,000 km	Race condition	NS
	4/F	34					
88	8/M	30.1 ± 7.2	Highly fit	Outdoor running	10,000 m	Race condition	P < 0.01
	7/M		Highly fit	Outdoor running	1,500 m		P < 0.01
	7/M		Highly fit	Outdoor running	100 m		P < 0.01
	5/M		Highly fit	Disk throwing			NS
89	10/M	24–41	Highly fit	Outdoor running	Marathon race	Race condition	P < 0.01
	5/M			Cycle ergometer	90 min	50% VO <sub>2</sub> max	P < 0.01
90	8/M	24.6 ± 2	Fit	Cycle ergometer	89 ± 1 min	65% watt max	P < 0.05
91	8/F	29.7 ± 4.0	Fit	Aerobic dance	45 min	High intensity	Significant
92	5/M	25 ± 2	Highly fit	Treadmill	30 ± 1 min/	Graded intensity to exhaustion	P < 0.001 (M + F)
	5/F	24 ± 2		Treadmill	29 ± 1 min		P < 0.05 (M);
				Outdoor running	57 ± 6 s/71 ± 8	Anaerobic trial	P < 0.01 (F)
					5–12 km	Aerobic trial	P < 0.05 (M + F)
25	10/M	23–36	Highly fit	Treadmill	6 × 10 min	50/60/70/80% VO <sub>2</sub> max	NS
						90% and 100% VO <sub>2</sub> max	P < 0.001
93	23/M	26.0 ± 0.9	Fit to highly fit	Rowing ergometer	9 min	Anaerobic exercise	P < 0.001
94	8/M	18–23	–	Cycle ergometer	25 min	50% VO <sub>2</sub> max	P < 0.05
95	32/M	24–63	Highly fit	Mountain running	46 km	rRace condition	P < 0.001
	9/F	25–55	Highly fit	Mountain running	46 km	rRace condition	NS
26	12/M	23.0 ± 0.8	Fit	Cycle ergometer	2 × 120 min	45% VO <sub>2</sub> max	NS
	11/M	21.4 ± 1.6	Unfit			60% VO <sub>2</sub> max	P < 0.05 (only fit)
27	6/M	21.8 ± 0.7	–	Cycle ergometer	<50 min	20 min 30%	NS
	6/F	23.7 ± 1.4				20 min 60%	P < 0.05 (F)
						Ride to exhaustion at 90% VO <sub>2</sub> max	P < 0.01 (F + M)

**Abbreviations:** NS, nonsignificant; HR, heart rate.

to capture endogenous neurotransmitter release in the CNS under experimental challenges (eg, pharmacological, cognitive, or sensorimotor). Currently, studies investigating neurotransmitter release cannot be performed with magnetic resonance imaging or other neuroimaging techniques. The

so-called “displacement” or “ligand activation studies” allow quantifying and localizing ligand binding changes by comparing rest and postexercise conditions.<sup>40</sup> Compared with animal work, the major advantage of studying central neurotransmission directly in human athletes is that



**Table 2** Papers reporting peripheral beta-endorphin values in relation to mood changes induced by exercise challenges

Publication	Endorphin increase	Mood elevation	Relationship
13	$P < 0.05$ (60% $\text{VO}_2$ max) NS (80% $\text{VO}_2$ max)	NS	No relationship
65	$P < 0.05$	NS	No relationship
30	$P < 0.0001$	Significant	Positive relationship
67	$P < 0.001$	NS	No relationship
3	$P < 0.01$	Significant	Positive relationship
77	NS	Significant	No relationship
81	$P < 0.003$	NS	No relationship

**Abbreviation:** NS, nonsignificant.

detectable binding changes can be tested for correlation with psychophysical effects, as detectable via standardized neuropsychological assessments. Moreover, compared with microdialysis studies in animals, which are restricted to selected brain areas, PET ligand studies provide quantitative measures of tracer binding in the entire human brain.

## Basic mechanisms and methodological limitations of PET ligand activation studies

Ligand activation studies derive quantitative measures of endogenous transmitter trafficking from ligand binding changes that result from competition at specific receptor binding sites in the brain. Although the temporal resolution of PET is low in comparison to other functional brain imaging techniques and does not suffice to capture real-time dynamics of transmitter release in the human brain, PET ligand activation studies allow calculating sustained tracer binding changes induced by previous exercise, ie, manifesting as prolonged changes in ligand binding status. It has to be pointed out that depending on the experimental challenge, either increased or decreased ligand binding changes have been identified in identical brain regions related to fundamentally different experimental challenges, ie, decreased binding reflecting enhanced release of the endogenous transmitter relative to rest,<sup>41</sup> or increased binding reflecting decreased release of the endogenous transmitter relative to rest.<sup>42</sup>

**Table 3** Papers reporting peripheral beta-endorphin values in relation to changes in pain perception induced by exercise challenges

Publication	Endorphin increase	Pain (hypoalgesia)	Relationship
59	$P < 0.0001$	$P < 0.01$	No relationship
31	$P < 0.001$	Significant	Positive relationship
3	$P < 0.01$	Significant	Positive relationship

The methodological details of PET ligand activation studies (eg, study designs, suitable PET tracers, ligand modeling approaches, etc) have been summarized extensively in a recent review article by Boecker et al<sup>40</sup> nonetheless, it is important to point out here again that PET is associated with radiation exposure, and, depending on the used tracer, with arterial cannulation for calculating the arterial input function. These methodological issues limit repeated PET acquisitions in the same patient, for instance PET scans under different experimental conditions, or longitudinal study designs. Usually, either separate acquisitions (eg, “baseline” scan and “experimental” scan in counterbalanced order) or one acquisition with an intermediate challenge are performed. In the context of exercise challenge studies, however, intermediate challenges (for instance, using a cycling device installed in the PET unit) are difficult to perform, as exercise challenges risk of being associated with severe head movement artifacts. This will be particularly limiting when intending to study the effects of high intensity or long intensity exercise challenges. Therefore, previous ligand activation work investigating exercise challenges has employed two separated scans, ie, one scan under baseline conditions and one scan immediately after exercise. In such a scenario, PET scanning typically starts with the injection of the radiotracer (to capture the tracer input function) and is continued for a prolonged time period (to capture specific neuroreceptor binding of the PET tracer using parametric and nonparametric kinetic modeling). It has to be considered, however, that enduring experimental challenges, such as continuous exercise, may induce receptor internalization or downregulation,<sup>43</sup> and can hardly be distinguished by means of PET from decreased binding due to enhanced endogenous transmitter release.

## PET ligand activation studies in the sport sciences

The first study to apply ligand PET to exercising humans was published in 2000 by Wang et al.<sup>44</sup> These authors studied 12 healthy volunteers using the dopaminergic PET tracer <sup>11</sup>C-Raclopride which binds to striatal D2-receptors.<sup>44</sup> Examining subjects twice allowed testing for the effects of a 30-minute treadmill exercise (average speed of  $8.7 \pm 0.5$  km/h;  $5.4 \pm 0.3$  mph) and at an inclination of  $3.3^\circ \pm 2^\circ$ ) upon dopaminergic release; however, no significant differences in binding at the D2 receptors were identified in this cohort after subjects exercised vigorously for 30 minutes. In the second previous study, which was performed at the Technical University Munich,<sup>41</sup> 10 trained athletes were scanned at rest and after 2 hours of

outdoor running using the nonselective opioidergic ligand 6-*O*-(2-[<sup>18</sup>F]fluoroethyl)-6-*O*-desmethyldiprenorphine ([<sup>18</sup>F]FDPN). These studies were performed to examine whether endogenous opioids are released after exercise and if so, whether such effects are linked to mood changes. In line with the “endorphin hypothesis”, this study identified significant reductions in [<sup>18</sup>F]FDPN binding in certain regions of the brain.<sup>41</sup> The strongest effects were seen in orbitofrontal cortex and in areas belonging to the limbic system, including the anterior cingulate cortex and the anterior insula. Although this work has been conducted in a rather small sample of *N* = 10 athletes undergoing 2 PET scans each, it is noteworthy that the displacement effects were clustered in brain regions associated with affective processing and current theories of opioid-mediated pleasure generation.<sup>45</sup> Regression analyses further indicated that the amount of endogenous opioidergic release was inversely correlated to the level of euphoria determined after exercise on visual analog mood scales.<sup>41</sup> We, therefore, conclude that ligand PET is able to noninvasively monitor transmitter release induced by exercise and to link these central neurotransmitter effects to behavioral measures that will inform researchers about the biology of exercise.

Based on this initial feasibility study, future PET work should try to image larger samples of athletes, possibly using subtype-selective tracers like <sup>11</sup>C-Carfentanil that do not require arterial cannulation. Furthermore, future work should attempt to stratify individual exercise challenges based on appropriate physical fitness tests. Moreover, careful monitoring of exercise load, use of appropriate neuropsychological tests designed for repeated testing, and incorporation of biomarkers like lactate, beta-endorphins, etc would advance PET ligand applications in the field of exercise research. Considering the duration of PET ligand studies, an improvement to our previous work would be to avoid any time delay between the end of exercise and the beginning of the study (injection of the PET tracer). This might be achieved with tracers that do not require arterial cannulation and may, thereby, be more suitable to detect the full range of neurotransmitter change in the immediate postexercise period. Of course, it is well conceivable that the extent of detectable neurotransmitter change may be further amplified with more strenuous exercise challenges, but these various effects will have to be systematically studied in the future. Having said this, the investigation of other neurotransmitter systems such as the endocannabinoid system<sup>46,47</sup> or the serotonergic system may represent alternative targets for future studies.

## Conclusion

The value of measuring plasma levels of neurotransmitters for understanding the neuro-psychophysiology of exercise is uncertain. Based on a literature survey spanning approximately 3 decades, we conclude that beta-endorphins levels in plasma after exercise challenges gives only limited information regarding putative central opioidergic effects and, thus, functional mechanisms of behavioral change. In particular, the amount of neurotransmitter detectable in the peripheral blood does not mirror the magnitude of central neurotransmission.

PET is proposed here as a powerful tool for human exercise research, with a hitherto unprecedented potential to unravel the “missing link” between neurotransmission in the CNS under exercise conditions and associated neurobehavioral effects in athletes. It is expected that PET will allow advancing our understanding of underlying neurochemical mechanisms involved in physical exercise. In particular, the correlation between neurochemistry and validated neuropsychological assessments has a strong potential to advance our knowledge about the central underpinnings of exercise-induced psychophysical effects. In conclusion, although still in its infancy, PET ligand activation studies provide a powerful tool for human exercise research.

## Disclosure

The authors report no conflicts of interest in this work. Henning Boecker holds an endowed professorship (Philips).

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