Chapter 8
Humoral Factors in Humans Participating in Different Types of Exercise and Training

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Abstract This chapter provides an overview on some effects of qualitatively and quantitatively different types of exercise stimuli on the blood concentration of neurotrophic factors, the hormone prolactin, and amino acids in humans. The findings of the research described are discussed in respect to their functional implications for neurogenesis and neurotransmitter systems in the brain.

8.1 Introduction

Qualitative and quantitative selective exercise stimuli are essential components in modern sports medicine (Hollmann and Strüder 2009), however, knowledge about the correlation between different types of physical exercise and brain health is still limited. The mechanisms through which exercise promotes brain health in humans have also been associated with humoral factors (Hollmann et al. 2003; Hollmann and Strüder 2000). The following chapter addresses aspects of the influence of physical exercise on these factors with special attention being paid to important neurotrophic factors as well as the hormone prolactin (PRL)

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and their impact on neurogenesis (see also Chaps. 1 and 2) as well as amino acids and their influence on neurotransmitters. Methodological aspects of the applied exercise stimuli, such as the type (e.g., endurance exercise, strength), the mode (e.g., graded, continuous), the duration (e.g., acute, chronic), or the intensity (e.g., aerobic, anaerobic) of the exercise regime as well as the training status of the investigated subjects, will be considered.

8.2 Neurotrophic Factors

Since it was discovered that new neurons are produced in specific human brain regions throughout one's lifetime (Eriksson et al. 1998), the relationship between altered growth factor function leading to modified neurogenesis has received increasing attention during the last 2 decades. While it has already been well established that impairment of synthesis and function of growth factors is an important causative factor in the pathogenesis of neuropathies, it is now increasingly recognized that this impairment plays a major role in the etiology of neuropsychiatric disorders in humans such as dementias and depression (Duman et al. 2000; Kempermann et al. 2008).

8.2.1 Brain-Derived Neurotrophic Factor

The neurotrophic factor brain-derived neurotrophic factor (BDNF) is one of the key regulators for increasing adult neurogenesis. It is well established that BDNF enhances synaptic transmission as well as long-term potentiation (LTP) and stimulates synaptic protein synthesis. BDNF has also been shown to promote differentiation of neural stem cells into neurons and to play an important role in preventing the death of newly generated cells. BDNF also supports the survival of neurons during stressful conditions such as ischemic insults and trauma (Vaynman and Gomez-Pinilla 2005).

Thus, BDNF promotes brain plasticity and functional changes. As a consequence, it is assumed that the maintenance of cerebral BDNF levels is of utmost importance. It is known that the peripherally produced BDNF, being able to cross the blood–brain barrier (BBB) in both directions, can exert supporting trophic effects on the CNS (Pan et al. 1998).

The production of BDNF is regulated by neuronal activity (Zafra et al. 1992). In addition, physiological stimuli such as exercise appear to be regulators for the BDNF levels (Neeper et al. 1995; Seifert et al. 2010). The regulation of BDNF through different types of exercise opens up an interesting avenue for research on the role of BDNF as a mediator in neuroplasticity (Fig. 8.1).

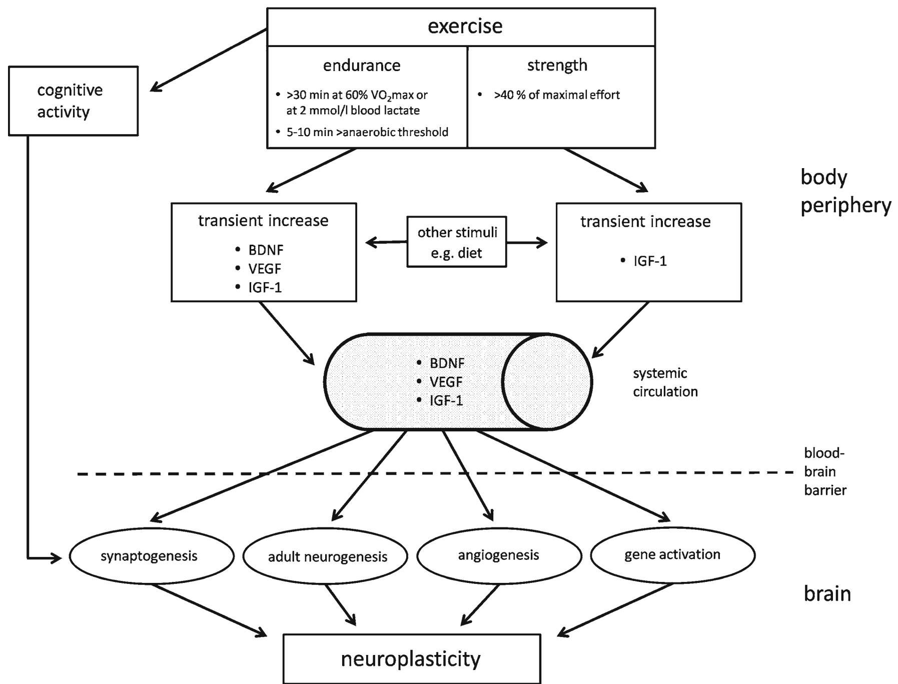

Fig. 8.1 Proposed mechanisms by which neuromuscular exercise affects neuroplasticity. The signaling of the organism's physical activity to the brain involves humoral but also directly neuronal modulation. Every physical activity already implies cognitive activity because activation in different brain regions, e.g., related to learning and memory, is required. The effects of exercise on neuroplasticity are mediated by the convergence and the synergy between growth factors like BDNF, IGF-1, and VEGF released during bouts of endurance exercise. Exercise can influence brain plasticity through the modulation of synaptogenesis, neurogenesis, and angiogenesis and also through activation of plasticity-related genes. *BDNF* brain-derived neurotrophic factor, *IGF-1* insulin-like growth factor 1, *VEGF* vascular endothelial growth factor

8.2.1.1 Effect of Acute and Chronic Exercise on Peripheral BDNF Levels

Acute Exercise

Different kinds of exercise regimes have been tested for their impact on the peripheral BDNF concentrations in humans. Incrementally graded exercise tests (GXT) are most usually used to test BDNF response. It was found that acute graded exercise elevates BDNF levels in a transient manner (Rojas Vega et al. 2006a; Ferris et al. 2007; Zoladz et al. 2008; Gustafsson et al. 2009; Laske et al. 2010).

The percentage increase depends on the exercise routines applied, with the associated differences in metabolic demands and the extent of effort. Rojas Vega et al. (2006a) reported that a GXT on a cycle ergometer up to exhaustion caused basal values to increase by approximately 40%. In a later study by Ferris et al. (2007), the peripheral BDNF levels during a GTX increased to a similar extent. In both studies the lactate concentration in the study participants upon reaching exhaustion was similar (approximately 10 mmol/L). Enhanced BDNF values after GXT were also reported for track or treadmill running (Winter et al. 2007; Laske et al. 2010), rowing (Gustafsson et al. 2009), and handcycling (Rojas Vega et al. 2008). After a graded submaximal cycling workout producing a lactate concentration of about 3 mmol/L, the increase in BDNF in women was found to be about 11% (Rojas Vega et al. 2012). The highest BDNF concentration was measured 5 min after completing the GXT session, with values returning to baseline levels within 10–15 min post exercise. All these studies using GXT suggest a link between BDNF elevations and exercise intensity.

Continuous high-intensity exercise of a few minutes duration caused an increase of BDNF levels of large variation. Some investigators report that high-intensity exercise increases BDNF concentrations in healthy subjects more effectively than low-intensity exercise (Rojas Vega et al. 2006a; Ferris et al. 2007; Castellano and White 2008; Gustafsson et al. 2009). According to studies so far, this was not the case, however, for diseased persons or persons with disabilities (Gold et al. 2003; Schulz et al. 2004; Rojas Vega et al. 2008; Gustafsson et al. 2009; Ströhle et al. 2010). Ferris et al. (2007) reported that an exercise intensity of 20% below the ventilatory threshold in healthy individuals caused no increase in BDNF levels, whereby at higher intensities (10% above the ventilatory threshold) increased BDNF blood concentrations were found. Winter et al. (2007) showed that short bouts of anaerobic exercise (two sprints over less than 3 min each with lactate levels above 10 mmol/L) increase BDNF levels to about 12% above baseline levels.

Exercise of longer lasting duration must be performed at an intensity low enough not to induce high lactate accumulation. No changes in BDNF concentrations were found in test persons after continuous cycling for 10 min; the corresponding lactate values were about 2 mmol/L (Rojas Vega et al. 2006a). An early study by Gold et al. (2003) reported that the BDNF levels were increased by 43% in multiple sclerosis patients as well as in healthy persons after 30 min cycling at 60% $\dot{V}O_2$max. Similarly, a study by Winter et al. (2007) showed that 40 min of low effort running (<2 mmol/L blood lactate) results in a transient increase of BDNF levels of about 15%. Other researchers reported elevated BDNF levels immediately after moderate endurance exercises such as cycling, stepping, and walking (Schulz et al. 2004; Tang et al. 2008; Ströhle et al. 2010).

Interestingly, all studies performed on subjects suffering from major depression, multiple sclerosis (MS), anorexia nervosa, or panic disorder exhibited lower values of basal BDNF compared to those in healthy untrained people (Gustafsson et al. 2009; Laske et al. 2010; Ströhle et al. 2010; Castellano and White 2008). This indicates either a reduced production of BDNF and therefore a reduced neuroprotection or an increased turnover of neurotrophins in the damaged CNS. Gold et al. (2003),

however, reported unchanged concentrations of BDNF in MS patients. Only one study investigated athletes with spinal cord injuries reporting that the intensity-dependent character of the BDNF response behaves inversely to that found in healthy individuals. This is because the BDNF levels here increased more due to acute exercise of a low to moderate intensity than to high-intensity prolonged exercise (Rojas Vega et al. 2008).

Only few studies used strength exercise as a stimulus for promoting BDNF release. The determination of exercise intensity is often done using the 1 repetition maximum (1RM) method. 1RM is the maximum amount of weight one can lift in a single repetition for a given exercise. Yarrow et al. (2010) examined 20 young men after strength exercises consisting of four sets with six repetitions at 52.5% of the 1RM and found a 32% increase in BDNF concentration. Rojas Vega et al. (2010) investigated the effect of different intensities of acute strength exercise on BDNF. Exercises at 40% and 110% of the maximum effort curve did not induce elevations in BDNF levels compared to pre-exercise values.

In summary, during acute exercise in humans the level of circulating BDNF is coupled to the intensity or duration as well as mode of the exertion. Acute endurance exercise at an intensity of 60% $\dot{V}O_2$max or at a lactate concentration of about 2 mmol/L, respectively, increases BDNF in the blood if the duration is at least 30 min. Exercise bouts of short duration also seem to increase BDNF concentrations if the intensity of the bouts is high. Strength exercise does not seem to affect plasma BDNF concentrations.

Chronic Exercise

In addition to factors such as age, sex, body weight, nutrition, and circadian rhythm, the concentration of BDNF also seems to be influenced by the training status (Lommatzsch et al. 2005). Most studies (Currie et al. 2009; Nofuji et al. 2008; Chan et al. 2008; Flöel et al. 2010; Gold et al. 2003) reported lower basal BDNF levels in athletes than in untrained persons. These lower basal BDNF levels might be attributable to a higher clearance rate of BDNF, or a greater increase in plasma volume due to physical training and the resulting lower circulating BDNF in the periphery. Schiffer et al. (2009) and Schulz et al. (2004) did not detect any differences between BDNF concentrations before and after an aerobic training period in the study participants at rest. Schiffer et al. (2009) applied a training period with exercise two to three times a week at 60% $\dot{V}O_2$max. However, four to seven training sessions per week at a higher percentage of $\dot{V}O_2$max resulted in greater exercise-induced levels of BDNF concentrations compared to before the training period (Baker et al. 2010). Thus, the frequency and intensity of training appear to influence the BDNF response to exercise, although further studies are needed to substantiate these results.

After strength training with untrained volunteers or recreational athletes, studies by Schiffer et al. (2009), Levinger et al. (2008), and Goekint et al. (2010) reported that basal levels of BDNF in test persons at rest remain unchanged, while

Yarrow et al. (2010) found changes in the responses to acute strength exercise. This study was conducted for 5 weeks with two groups using two exercises on strength-training devices with different intensities for each group. The studies by Schiffer et al. (2009), Levinger et al. (2008) and Goekint et al. (2010) applied a traditional training method using strength-training devices for a longer training period of 10–12 weeks. Training with a complete body workout was conducted three times per week.

In summary, based on the present data, no reliable conclusions can be drawn on the effect of strength training on the basal concentration of BDNF.

8.2.1.2 Factors Influencing BDNF Response to Exercise and the Functional Implications

The effect of lactate is one of the possible underlying mechanisms that could stimulate BDNF release after acute high-intensity exercise with considerable lactatemia. A recent study by Schiffer et al. (2011) investigating the influence of a lactate clamp on BDNF concentration with the study participants at rest showed an increase of peripheral BDNF concentrations. The sodium lactate infusion raised the lactate values to 10–15 mmol/L without acidosis but with alkalosis. The lactate concentrations reached were similar to those that occurred during exercise workouts which induced BDNF augmentation. Recently, it was also shown that buffering the decrease of pH during a maximal ramp test on a cycle ergometer does not reduce the exercise-induced BDNF increases (Rojas Vega et al. 2012). In this study, the infusion of bicarbonate attenuated the pH and base excess values, whereby the lactate values of 10 mmol/L remained unaffected. As the study by Schiffer et al. (2011), with test subjects at rest, led to alkalosis and the investigation by Rojas Vega et al. (2012) with subjects undergoing high-intensity exercise led to acidosis, it seems likely that the pH or base excess values do not play a decisive role in inducing BDNF release. Across both studies, the best correlations with BDNF concentrations were observed for lactate. These results suggest that lactate supports the release of BDNF at its major secretion area in the central nervous system during exercise. Interestingly, a portion of BDNF is released from the human brain during exercise (Rasmussen et al. 2009), however, peripheral sources can also contribute to increases of BDNF in the blood (Lommatzsch et al. 2005; Tang et al. 2008; Matthews et al. 2009). Because the actions of BDNF in the CNS can be due to the growth factor of central or peripheral origin, in this review we refer to its effects in the CNS without attributing a source.

The regulation of BDNF through exercise opens up an interesting perspective for the function of BDNF as a mediator in neuroplasticity in the CNS. The increase of the serum BDNF concentration as a result of exercise seems to be of importance for maintaining proper brain functions (Cotman and Berchtold 2002). A connection between peripheral BDNF, with its ability to cross the BBB, and the central action of BDNF is a necessary prerequisite for this effect. There is mounting

evidence that a deficiency in BDNF plays a critical role in the pathophysiology of mood disorders such as depression and neurodegenerative diseases, i.e., Alzheimer's and dementia (Kempermann et al. 2008).

8.2.2 Insulin-Like Growth Factor 1

Insulin-like growth factor 1 (IGF-1) is important for anabolic effects of exercise and training, i.e. muscle hypertrophy. It is also a potent neurotrophic factor promoting neuronal survival and differentiation (Leventhal et al. 1999). Peripheral IGF-1 has been demonstrated to play an important role in neurogenesis in the hippocampus (Aberg et al. 2000; Trejo et al. 2001). There is an abundant presence of receptors in the neuronal tissues of the CNS, while synthesis of IGF-1 protein from adult central neurons is very low, which suggests that the adult brain takes up IGF-1 from sources outside the brain (Bondy and Lee 1993). The biological process of circulating IGF-1 influences the CNS via a range of different paths. It is also assumed that peripheral IGF-1 is important for mediating effects of other growth factors in the CNS. For example, hippocampal expression of BDNF is enhanced in the presence of IGF-1 (Ding et al. 2006). Moreover, IGF-1 modulates a variety of homeostatic processes in the CNS, processes which are promoted by exercise and involve angiogenesis (Lopez-Lopez et al. 2004). A blocking of the peripheral IGF-1 resulted in a significant reduction in the production of new brain capillaries due to the inhibiting effects of the vascular endothelial growth factor (VEGF), a molecule prominently involved in promoting blood vessel growth.

8.2.2.1 Effect of Acute and Chronic Exercise on Peripheral IGF-1 Levels

It has been shown that (1) exercise stimulates the release of IGF-1 in the liver, resulting in an elevated brain uptake of IGF-1 (Carro et al. 2000), and (2) peripheral IGF-1, by crossing the BBB, increases the presence of IGF-1 mRNA in the hippocampus (Ding et al. 2006; Fig. 8.1). The relevance of this mechanism is underscored by the fact that the administration of peripheral antibody-IGF-1 blocks the exercise-induced neurogenesis in the dentate gyrus (Trejo et al. 2001). Restoring IGF-1 levels through an exogenous administration fosters functional recovery, thus helping to rectify learning deficits and promoting neurogenesis and neuroplasticity. The use of exogenous IGF-1 indicates that it is essential but not sufficient to mimic all the effects of exercise, which provide neurotrophic support and influence plasticity-related processes in the brain (Llorens-Martin et al. 2009). The action of exercise-induced IGF-1 augmentation on the brain in humans could be facilitated by changes in the transport proteins and by changes in the BBB permeability during exercise.

Acute Exercise

Several studies have reported increased levels of IGF-1 in humans after acute exercise (Bang et al. 1990; Cappon et al. 1994; Schwarz et al. 1996). After 10 min of cycle ergometer exercise at intensity above the lactate threshold, IGF-1 increased to 14% above the pre-exercise levels and remained elevated for 20 min after cessation of the exercise period (Cappon et al. 1994). Rojas Vega et al. (2012) have shown in women that 10 min of aerobic cycling increased circulating IGF-1 levels by 16%, and this augmentation was maintained for at least 10 min into the recovery phase. Schwarz et al. (1996) reported that the IGF-1 levels increase after low- and high-intensity continuous exercise periods. During a period of cycling for 10 min at levels below the anaerobic lactate threshold, the IGF-1 concentrations increased by 7%, while high-intensity exercise raised these levels by 13%. Consistent with these findings, Bang et al. (1990) reported an increase in IGF-1 concentration levels in healthy subjects of 26% after 10 min of exercise. Rojas Vega et al. (2008) also observed an increase of circulating IGF-1 levels of 7% in disabled athletes after 42 km of hand cycling at an intensity of 65% of $\dot{V}O_2max$. Hagberg et al. (1988), however, did not find an increase in IGF-1 in long-distance runners after a 60-min exercise period on the treadmill at an intensity of 70% of $\dot{V}O_2max$. However, only slightly increased levels of lactate were observed during exercise, indicating a low physiological stress for these athletes, probably causing these contrary findings.

A study by Rojas Vega et al. (2010) revealed that high- and low-intensity strength exercises increased the circulating levels of IGF-1. Although increases in IGF-1 were found for both exercise intensities, the two study intensities exhibited different post exercise responses. Specifically, only the low exercise intensity exhibited continuous IGF-1 augmentation during the 10-min recovery phase, an effect not found for the high-intensity condition. This response pattern may be related to an enhanced clearance of IGF-1 following high-intensity strength exercise. Interestingly, this study revealed that only low-intensity exercise was required to achieve a large increase of circulating IGF-1. Compared with studies applying a continuous low-intensity endurance exercise workout, low-intensity strength exercise elevated IGF-1 concentration to a much greater extent (28%). Further, Schwarz et al. (1996) indicated that high-intensity cycling produced an IGF-1 increase of 13%, which correlated with the values found after high-intensity strength exercise in a study by Rojas Vega et al. (2010).

Chronic Exercise

A number of cross-sectional analyses have shown that the presence of circulating IGF-I correlated with the level of fitness (Poehlman and Copeland 1990), although the results of different exercise training studies have given inconsistent values of basal IGF-I concentrations (i.e., unchanged (McCall et al. 1999), increased (Koziris et al. 1999), and decreased (Eliakim et al. 1998)). The variance in these findings

may result from differences in the extent and intensity of the training programs. The decreased basal IGF-1 concentrations after short-term (5 week) interval endurance training correlated with a negative energy balance during the training intervention (Eliakim et al. 1998). On the other hand, it seems that a high training volume is most effective for increasing basal IGF-1 levels, e.g., a high intensive cycling race lasting 3 weeks consisting of 21 stages over a distance of 3,518 km as well as a 4-month training program with a weekly workload of 500 km resulted in significant augmentations (Manetta et al. 2003; Chicharro et al. 2001).

Basal levels of IGF-1 were found to be unchanged after short-term strength training (<10 weeks) (McCall et al. 1999; Kraemer and Ratamess 2005; Izquierdo et al. 2006), whereas long-term strength training (>10 weeks) resulted in increases in the IGF-1 basal concentrations (Koziris et al. 1999; Borst et al. 2001 and Marx et al. 2001). However, some long-term studies also reported unchanged IGF-1 levels (Walker et al. 2004).

Schiffer et al. (2009) reported decreased basal IGF-1 levels after 12 weeks of intensive strength training where extensive scatter in basal IGF-1 concentration was found for different individuals. Finally, acute overreaching resulting from a high-volume strength training has been shown to reduce basal IGF-1 concentrations by 11% (Raastad et al. 2003), whereby the values returned to baseline levels when normal training was resumed. Considered together, these results indicate that chronic adaptations of basal IGF-1 levels after training may also be affected by the volume and intensity of the strength training (Kraemer and Ratamess 2005; Raastad et al. 2003). On the other hand, studies evaluating the effects of prolonged training on acute exercise-induced IGF-1 responses showed that the circulating IGF-1 level was unchanged after 12 weeks of strength training (McCall et al. 1999). In this study, however, the IGF-1 values were corrected for plasma volume decrease. This is a somewhat questionable procedure as the uncorrected concentration is what the tissue "senses" and which mediates the effects of exercise on the target tissues (Cappon et al. 1994).

8.2.2.2 Factors Influencing IGF-1 Response to Exercise and the Functional Implications

The majority of circulating IGF-1 is bound to binding proteins (BP). The biological effects of IGF on the nervous system are mediated by the type I of IGF receptors. The function of the binding protein is to regulate the IGF bioavailability by hindering degradation, by modulating the levels of free IGF and possibly, by delivering IGF to target tissues. The most abundant BP is IGFBP-3, which is synthesized in the liver, reaching its peak circulating levels during puberty and decreasing with increasing old age. Interestingly, there is a marked IGFBP-3 protease activity during pregnancy, which appears to play a key role in the higher circulating IGF-1 bioavailability. The pregnancy-associated cleavage patterns are thought to be responsible for the local release of bioactive IGF-1 in humans when subjected to high-intensity exercise.

Schwarz et al. (1996) showed that IGFBP-3 increases its proteolytic activity during heavy exercise simultaneously with a peak increase in IGF-1. Increases in circulating IGF-1 after exercise might also reflect increases in hepatic IGF-1 production, which is assumed to be unrelated to exercise-induced secretion of growth hormones (GH) (Bang et al. 1990; Schwarz et al. 1996), because the IGF-1 reaches peak levels before the GH levels peak. Furthermore, Bang et al. (1990) showed that exercise induced increases in IGF-1 levels not only in healthy people but also in persons with a pituitary insufficiency.

Only a few studies have examined the adaptation of circulating IGFBP-3 to strength training. Whereas Elloumi et al. (2005) and Borst et al. (2001) reported a reduction of basal IGFBP-3 after long-term strength training, a study by Izquierdo et al. (2006) showed an increase. Elloumi et al. (2005) proposed that the decreased IGFBP-3 together with the elevated levels of IGF-1 in the test person at rest is an indicator for overtraining. The study by Izquierdo et al. (2006) suggested that an increase in IGFBP-3 concomitant with decreased IGF-1 levels in the test person at rest might be a compensatory process in the body to preserve IGF-1 availability.

Nemet et al. (2004) found that the energy balance is a regulating parameter, insofar that training plus an energy intake deficit causes a reduction in IGF-I levels, whereas training plus energy intake excess results in increased IGF-I concentrations. These results are in line with results by Smith et al. (1987), which showed that acute exercise that produces a negative caloric balance also causes an IGF-1 decrease, analogue to an equivalent restriction in caloric intake without exercise.

The potential beneficial stimulus on the brain might be related to repeated exercise-induced elevations of IGF-1 during training programs. Endurance and strength training also seem to increase basal IGF-1 concentrations if volume and/or intensity of training are high. Low-intensity strength training already induces high IGF-1 augmentation. Thus, strength exercise of this particular intensity should be considered when defining exercise prescriptions aimed at benefiting brain health throughout a subject's life span.

8.2.3 Vascular Endothelial Growth Factor

It has been suggested that adult neurogenesis occurs within the so-called angiogenic niche (Hsieh and Eich 2010). Within this niche, endothelial cells are regulators for self-renewal of stem-like cells through the release of trophic factors. Thus, an alteration in the vascular microenvironment affects neurogenesis. VEGF is primarily a potent mitogen of endothelial cells (Leung et al. 1986). There is growing evidence, however, that VEGF also induces neurotrophic and neuroprotective effects (Ding et al. 2004). An artificially induced elevation of VEGF was shown to increase adult neural progenitor cell differentiation into neurons in the adult hippocampus (Fabel

et al. 2003), an effect associated with enhanced cognition (Cao et al. 2004). It has been shown in humans that exercise increases angiogenesis in the dentate gyrus (Pereira et al. 2007). Theoretically, this might improve access to growth factors in the brain. Angiogenesis is a vital adaptation to chronic exercise whereby the exercise-induced enhanced VEGF levels has been proposed as a stimulus for this process (Prior et al. 2004).

8.2.3.1 Effect of Acute and Chronic Exercise on Peripheral VEGF Levels

VEGF is produced by skeletal muscle cells and can be released into the blood circulation during exercise (Hiscock et al. 2003). A peripheral blockade of VEGF was shown to abolish exercise-induced neurogenesis, while the baseline levels of neurogenesis were not affected (Fabel et al. 2003). An association between neurogenesis and VEGF in humans has not yet been proven. Notwithstanding, an in vivo correlation between neurogenesis and angiogenesis was recently demonstrated in exercising humans (Pereira et al. 2007). This study found that exercise selectively affects angiogenesis in the hippocampus, which in turn correlated with the cardiopulmonary and cognitive function.

Acute Exercise

Several studies have shown that circulating VEGF is increased by acute exercise (e.g., Kraus et al. 2004; Rojas Vega et al. 2012). After 10 min of acute submaximal exercise at lactate concentration of about 3 mmol/L, the VEGF levels increased to 19% above those levels of the test person at rest (Rojas Vega et al. 2012). Submaximal exercise of longer duration induced an even higher increase of circulating VEGF (Kraus et al. 2004). The increased levels persisted from 20 min up to 2 h after cessation of exercise (Kraus et al. 2004; Rojas Vega et al. 2012). The transient nature of the VEGF response to a single exercise routine appears to be coupled to the increase of mRNA (Richardson et al. 1999) as well as the decrease of VEGF protein in the skeletal muscle immediately after exercise (Kraus et al. 2004). Thus, the disappearance of VEGF from skeletal muscle results in an increase in circulating VEGF. This effect is involved in the well-documented formation of new capillaries, because the VEGF induces mitogenesis in endothelial cells and therefore functions as an angiogenic factor.

Only few studies have examined the effect of strength exercise on VEGF concentrations. Jozsi et al. (2000) demonstrated that acute strength exercise (3×8 repetitions of five lower body exercises at 80% of the 1RM) enhances the increase of VEGF mRNA in human muscles. In accordance with these data, Richardson et al. (1999) reported that VEGF mRNA levels are augmented in human skeletal muscles after only 30 min of knee-extensor exercise at 50% of the 1RM. In this study, however, a GXT to exhaustion in advance was part of

the exercise workout, therefore making it impossible to separately quantify the effects of the two kinds of stimuli on VEGF. The effect of isokinetic strength exercises on VEGF concentrations was evaluated by Rojas Vega et al. (2010). Each test person was tested on 1 day at an exercise load equal to 40% and on another day at 110% of the averaged individual maximal effort curve, respectively. At both intensities, however, the strength exercise did not increase the levels of serum VEGF at any time during the trials.

Chronic Exercise

In endurance-trained people no differences were found in the basal circulating VEGF concentrations compared to sedentary people (Kraus et al. 2004). An investigation by Gustafsson et al. (2002), however, revealed a decrease in the basal VEGF values after a 10-day training program. The conflicting results of the studies might have stemmed from the initial physical condition of the subjects. The athletes in the study by Kraus and coworkers had completed a long training period (>6 month) and the training volume was high (6 days/week), while the subjects in the study by Gustafsson et al. (2002) were only subject to a training period of 10 days. Kraus et al. (2004) reported that acute exercise increased the VEGF levels at 0 and 2 h postexercise in endurance athletes but not at any time in sedentary individuals. There was no difference, however, in the VEGF levels between the two groups at any other point in time. An analysis of the individual peak postexercise VEGF levels revealed that exercise increased VEGF levels independent of the training status.

8.2.3.2 Factors Influencing the VEGF Response to Exercise and the Functional Implications

Factors such as the age and gender of subjects as well as a variety of medical/physical conditions can influence the response of VEGF levels to exercise. Breen et al. (1996) reported a greater increase in the levels of VEGF mRNA in rats, when exercised in a hypoxia environment. In contrast, an in vivo study by Kraemer and Ratamess (2005) found that VEGF gene expression is not sensitive to tissue hypoxia. The response of VEGF levels to acute exercise appears to be mediated by the reduction of intracellular partial pressure of oxygen (pO_2) occurring during the transition period from rest to exercise. The VEGF mRNA levels, however, were not enhanced when exercise was performed under hypoxia (Richardson et al. 1999). Apparently, there is an intracellular "pO_2-threshold" beyond which no enhanced angiogenic stimulus is produced. Submaximal and maximal exercise under normoxia appears to reach this threshold and therefore may induce a neuro-angiogenic stimulus. Furthermore, prolonged exercise during severe hypobaric–hypoxia (after a high altitude marathon run-up to 4,722 m) decreased VEGF serum concentrations (Gunga et al. 1999). In contrast, intensive swim training for 21 days at 1,886 m enhanced

VEGF serum levels, whereby it is difficult to distinguish between effects of altitude and those of exercise. Hypoxia per se, however, does not seem to play a decisive role in exercise-induced increases of circulating VEGF levels.

VEGF concentrations in pregnant women were not detectable with the subject at rest or after graded exercise up to a heart rate of 150 bpm (Rojas Vega et al. 2012). This may indicate that enzymatic (probably protease) activity occurs or is substantially increased in the blood circulation, which degrades the VEGF protein. This suggests that a possible degradation of peripheral VEGF during late gestation suppresses the action of this factor and is not influenced by exercise. Because it has been suggested that elevated levels of VEGF during pregnancy may be involved in the pathogenesis of preeclampsia, undetectable levels of VEGF after exercise may reflect an important physiological adaptation in pregnant women, which reduces the risk of the onset of preeclampsia.

Muscle VEGF protein, VEGF mRNA, and muscle vascularization with a person at rest is lower in the elderly than in young men and women. This age-related decline contrasts with the response to acute exercise. That is, after 45 min of cycle ergometer exercise at 50% of $\dot{V}O_2$ max, the VEGF protein and VEGF mRNA levels increased, independent of age (Croley et al. 2005). This response to exercise suggests a compensatory mechanism with age for improving the diffusive capacity of the muscles (Charifi et al. 2004) and seems to be an important biological mechanism in promoting neuroangiogenesis, and thus protecting the brain from a decline in neurogenesis with age. VEGF may constitute the link between neurogenesis and angiogenesis in exercising humans, and mediate neurotrophic and neuroprotective properties. The optimal dose and duration of exercise for the promotion of angiogenesis through increases of circulating VEGF correspond to aerobic exercise lasting longer than 10 min, which is also typically recommended in exercise programs aimed at promoting health. More studies are required for strength exercises. It can be assumed, however, that acute strength exercise at an intensity of >50% of the individual maximal effort enhances the VEGF levels.

8.2.4 Analytical Aspects for the Neurotrophic Factors BDNF, IGF-1, and VEGF

Blood for measurements of neurotrophic factors may be obtained from veins or arteries. The specimen of choice is venous blood, which is usually taken from the brachial vein. Samples should be collected in venipuncture tubes which were prechilled in ice water. Either serum or plasma samples can be used. In the case of plasma, heparin or ethylenediaminetetraacetic acid (EDTA) is used as an anticoagulant. With the addition of anticoagulants to the blood, plasma can activate blood platelets and change the concentration of the constituents to be measured (Schneider et al. 1997).

Care is required when taking the blood sample, its preparation (especially the time frame until samples are frozen) and storage, because these methodological aspects influence the humoral values. Venous occlusion from the use of a tourniquet changes the concentration of the blood components, mainly peptides and proteins, when the stasis is more than 3 min (Young and Bermes 1986). After blood collection, venipuncture tubes must be immediately placed on ice until processed. Many proteins are thermally labile and serum or plasma should be stored and frozen immediately. When additive-free tubes (serum) are used, the time for blood clotting prior to serum extraction and the temperature at which blood clotting occurs must be taken into account to ensure complete clotting and platelet degranulation in the sample. Serum and plasma are obtained by centrifugation of the samples tubes for 10 min at 3,000 rpm and 4°C. Supernatants must be aliquoted and stored at −80°C until analysis. Possible interference of the specimen collection and storage has been well documented for BDNF. A study by Katoh-Semba et al. (2007) found that BDNF in serum is gradually released from platelets at 4°C, while it begins to degrade immediately at a room temperature of 26°C. Furthermore, Trajkovska et al. (2007) showed a decrease of BDNF concentration in blood stored at 4°C, which did not occur at −20°C, whereas the storage of blood serum at −20°C resulted in a reduction of BDNF concentration over time. These results suggest that BDNF storage in platelets hinders degradation for prolonged periods subsequent to extracting the blood. However, plasma samples also allow clotting if stored for prolonged periods after collection.

The concentrations of serum BDNF are approx. 200 times higher than those found for plasma BDNF, which indicates that BDNF is stored in the platelets. Platelets circulate for up to 11 days in peripheral blood, whereas BDNF protein circulates in plasma for less than an hour. Thus, platelet BDNF might be a long-term marker of varying plasma BDNF concentrations (Lommatzsch et al. 2005). However, a relationship between serum BDNF levels and BDNF concentrations in the CNS has been shown in several animal studies and also in clinical studies of patients with mood disorders (Karege et al. 2002, 2005; Lang et al. 2004; Shimizu et al. 2003). In these studies serum BDNF but not plasma BDNF correlated with the severity of depression. Consequently, serum samples are preferred for analysis of BDNF.

For the analytical procedure, the assay technique for serum or plasma BDNF, VEGF, and IGF-1 is the enzyme-linked immunosorbent assay ELISA. ELISA kits from several manufacturers are available (e.g., ChemiKine, Promega, R&D System, Phoenix pharmaceuticals). All measurements should be performed in duplicate and according to the instructions of the manufacturer.

8.3 Prolactin

Interestingly, is has been shown that PRL is the only hormone which augments neurogenesis in the subventricular zone (SVZ) by stimulating the proliferation of neural stem cells and their differentiation into neurons (Shingo et al. 2003). A reduced level of neurogenesis was found in mice with a deficiency of PRL receptors. Peripheral as well as a central infusion of PRL induced neurogenesis in the SVZ.

These findings suggest that alterations of PRL during exercise might also be associated with increased neurogenesis.

The level of PRL is known to increase in response to physical stress such as exhaustive exercise or sexual activity (Noel et al. 1972; Brisson et al. 1981; Exton et al. 2001). PRL is synthesized in lactotrophic cells in the anterior pituitary and secreted in episodes. This process is controlled by PRL releasing (PRFs) and inhibiting factors (PIFs). Pituitary PRL acts as hormone via classic endocrine pathways. PRL is also produced at numerous extrapituitary sites where it is regulated by local factors, and thus can act in a direct fashion as a growth factor, neurotransmitter, or immune-regulator in an autocrine or paracrine manner (Bole-Feysot et al. 1999; Ben-Jonathan and Hnasko 2001). Whereas the physiological function of PRL in reproduction processes and in the induction of maternal lactogenesis is well established, the role of PRL secretion in males still has to be clarified. The release of PRL in humans is subject to the action of dopamine (DA) as the main PIF (Ben-Jonathan and Hnasko 2001). Increased DA synthesis and metabolism were shown during and following exercise (Meeusen and de Meierleir 1995), suggesting that exercise-induced PRL release is not related to alterations in the dopaminergic system activity and PRFs, such as the thyrotropin-releasing hormone (TRH) or serotonin (5-HT), are responsible for the acute secretory activities.

5-HT is one of the most prominent excitatory neurotransmitters for stimulating PRL release (Reichlin 1998; Tuomisto and Manisto 1985). 5-HT neurons originating in the dorsal raphe nuclei project to the hypothalamus and induce PRL release from the anterior pituitary by activating central 5-HT_{1A} and/or 5-$HT_{2A/2C}$ receptors (Van de Kar et al. 1996). Because the administration of tryptophan (TRP), 5-hydroxytryptophan (5-HTP), 5-HT, or 5-HT-releasing drugs increased secretion of PRL in rats, while the destruction of serotonergic neurons in dorsal raphe nuclei prevented PRL increase after 5-HT releasers were administered or it was induced by suckling (Van de Kar et al. 1996), the physiological role of 5-HT on PRL secretion has been used as a hormonal probe for 5-HT activity after exercise (Strüder and Weicker 2001). Similarly, based on the findings that 5-HT plays an important role for the PRL response to stress and considering that 5-HT is involved in the pathophysiology of mood and affective disorders, PRL has been used to characterize such alterations. A blunted PRL response to serotonergic challenges is an endocrine abnormality described in depressed patients (Mayberg et al. 2002).

8.3.1 Effect of Acute and Chronic Exercise on Peripheral PRL Levels

Acute Exercise

Different exercise workouts have been used to specify PRL response to exercise. Intense acute physical exercise is a strong stimulus for PRL secretion (De Meirleir et al. 1985a). No PRL increases were found after short-term exercise at 50% $\dot{V}O_2max$ (Luger et al. 1992) or 65% $\dot{V}O_2max$ (Strüder et al. 1998b).

Exercise performed at higher intensities (>70% $\dot{V}O_2max$) raised PRL after 30 min (Luger et al. 1992) as well as after 15 min at exercise intensity of 80% $\dot{V}O_2max$ (Keizer et al. 1987). Increases of PRL levels were found already after two consecutive 400-m runs with 2 min rest in between (Rojas Vega 2001) and after 7.5 min of incremental cycling to exhaustion in athletes (Rojas Vega et al. 2006a). The effect of a single bout of high-intensity endurance exercise (treadmill running at about 100% $\dot{V}O_2max$) on the PRL concentration in 22 males was studied by Daly et al. (2005), whereby a sharp increase of PRL was found at the point of volitional fatigue. Elevated PRL concentrations were observed up to 60 min after cessation of exercise.

For PRL secretion during exercise, duration and intensity are of importance (Fig. 8.2). Low-intensity exercise usually induced a significant PRL increase when the duration of exercise was prolonged, e.g., cycling at a lactate concentration of about 2 mmol/L (Strüder et al. 1997) or after a marathon run (Tanaka et al. 1986). Strüder et al. (1997) excluded glucose availability as a trigger stimulus of PRL secretion during exercise as infusion of glucose alone or glucose with insulin during exercise did not affect its release. The authors proposed that exercise-induced hyperprolactinemia during prolonged exercise is rather related to the increase of the free tryptophan (TRP) to branched-chain amino acids (BCAA) ratio. This increase favors free TRP uptake at the competitive L-carrier of the blood–brain barrier which accounts for augmented 5-HT synthesis in the brain (Fig. 8.3).

Chronic Exercise

Studies investigating the effects of training on PRL secretion have shown inconsistent results. Specifically, Smallridge et al. (1985) reported that plasma PRL response after TRH challenge was enhanced after endurance training, suggesting that secretion of PRL is sensitive to the training level. In contrast to these results, studies by Strüder et al. (1998b) showed that the acute PRL response to 30 min of cycling did not differ between sedentary and endurance-trained elderly subjects. Neither basal plasma hormone concentration nor the response to TRH stimulation differed between both groups, suggesting that this specific PRL regulation mechanism was not altered by endurance training. On the other hand, Jakeman et al. (1994) used PRL as a hormone marker of the 5-HT function following oral administration of an acute dose of a 5-HT agonist and found a lower peak PRL concentration as well as a lower total release in endurance athletes compared with untrained subjects. This lower neuroendocrine response was suggested to be caused by a downregulation of central 5-HT receptor function.

Alternatively, an excessive increase in training volume over 4 weeks caused an elevation of the basal PRL level in young endurance athletes, while a moderate training over 3 weeks in recreational athletes led to lower basal PRL values (Strüder and Weicker 2001). Furthermore, Lehmann et al. (1992) reported that an increase in training volume, designed to induce an overtraining syndrome, did not lead to a change in the basal PRL concentration; the exercise-induced PRL level, however, was slightly decreased after absolving the training program.

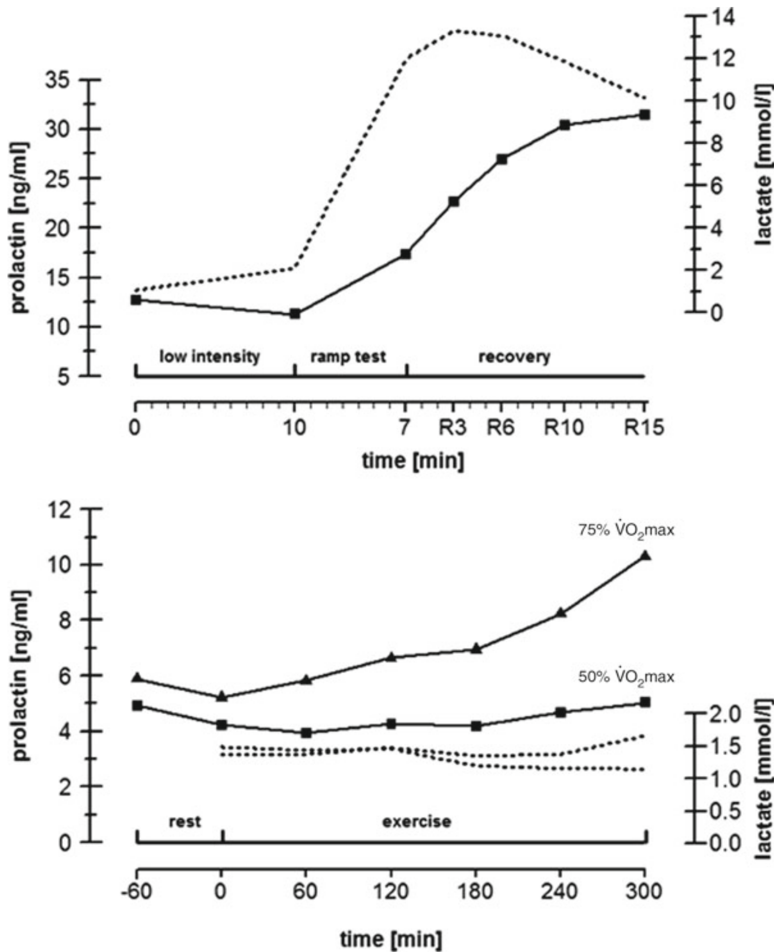

Fig. 8.2 Effects of exercise on prolactin (PRL). Exercise was performed in two different modalities: incremental exercise to exhaustion (*top*) or constant low- and moderate-intensity exercise of longer duration (button). Lactate values (*dotted lines*) at the end of incremental test (ramp test) are above the anaerobic threshold (AT) while lactate values at low/moderate-intensity exercise are below AT. The closed lines show the corresponding PRL concentration in the blood. Exercise exceeding the intensity of AT raises PRL levels. Exercise of long duration at moderate intensity stimulates PRL release. During 300 minutes of exercise at constant low or constant moderate intensity lactate values (*dotted lines*) do not differ between trials and are below the anaerobic threshold. Closed lines show the corresponding PRL concentrations at the respective exercise intensities. (Modified from Strüder et al. 1997; Rojas Vega et al. 2008)

Studies investigating the effects of chronic strength training (Häkkinen et al. 1985) or a single session of strength training (Bosco et al. 2000) on PRL levels did not reveal significant changes in the basal levels of the hormone. Similarly, Hickson et al. (1994) reported unchanged basal plasma PRL levels in males and females after 9 weeks of heavy strength training, despite the fact that PRL concentrations were assessed directly after acute bouts of very heavy strength exercises in males.

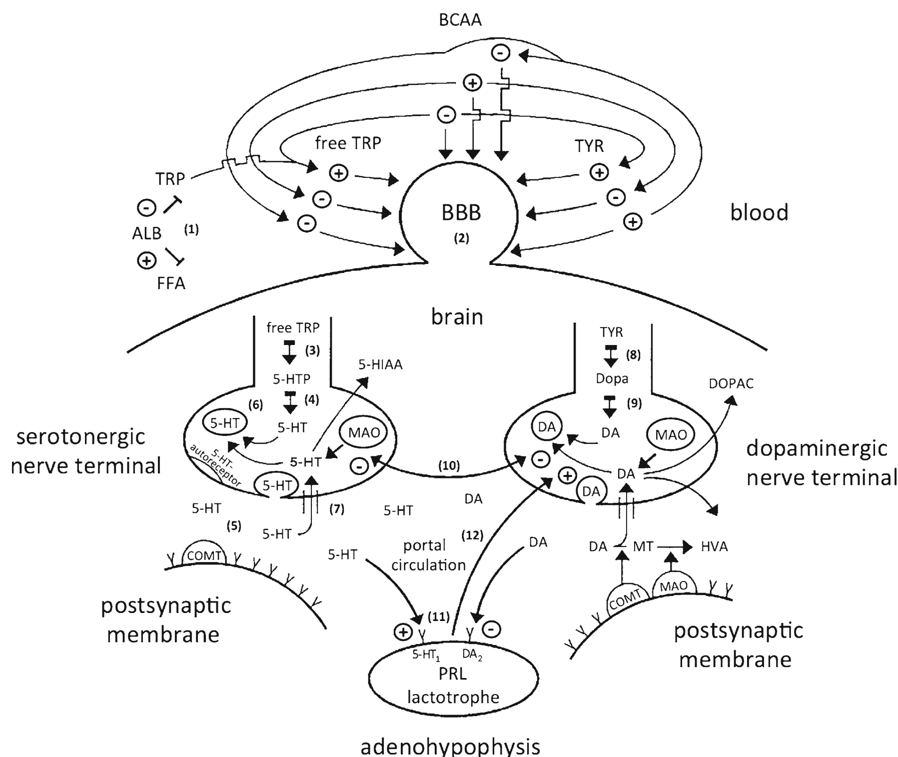

Fig. 8.3 Relation between the monoaminergic system and the lactotrope system of the adenohypophysis: During endurance exercise augmentation of plasma FFA induces an increment of free TRP due to displacement of TRP from ALB (1). Plasma free TRP, BCAA, and TYR compete for transport over the L-carrier at the BBB (2). Exercise-induced decline of BCAA favors the entry of free TRP and TYR into the brain. Administration of BCAA reduces free TRP and TYR transport into the brain while TYR administration reduces free TRP and BCAA transport over the BBB. In the brain free TRP is converted to 5-HTP by TRP-hydroxylase (3), the unsaturated rate-limiting enzyme in the synthesis of 5-HT. 5-HTP is decarboxylized to 5-HT (4). 5-HT can be released (5) or stored (6). 5-HT that is not stored in vesicle is degraded by MAO to 5-HIAA. The 5-HT transporter regulates the reuptake of 5-HT from the synaptic cleft (7). Paroxetin administration prevents reuptake of 5-HT into nerve terminals. TYR is transported into the neurons and converted to DOPA by TYR-hydroxylase (8), the largely saturated rate-limiting enzyme in DA synthesis. DOPA is decarboxylated to DA (9). Newly synthesized DA can be released or stored. Following the breakdown by COMT and/or MOA, DA is transformed into HVA and DOPAC. 5-HT and DA activity may inhibit each other (10). 5-HT and DA released at the outer layer of the medial eminence enters the portal circulation, where it may act directly on the mammotrophic substances of the anterior pituitary. 5-HT bound to 5-HT_1 receptors has stimulating influence while DA bound to DA_2 receptors inhibits PRL release (11). PRL, via short-loop feedback, elevates DA turnover (12). *ALB* albumin, *BBB* blood–brain barrier, *COMT* catechol-o-methyl transferase, *DOPA* dihydroxyphenylalanine, *DOPAC* 3,4-dihydroxyphenylacetic acid, *HVA* homovanillic acid, *MAO* monoamine oxidase, *5-HIAA* 5-hydroxyindoleacetic acid, *5-HTP* 5-hydroxytryptophan) (Modified from Strüder et al. 1998a)

8.3.2 Factors Influencing the PRL Response to Exercise and the Functional Implications

PRL exhibits a circadian rhythm with peak values in the early morning hours with circulating PRL levels lowest at midday. Approximately 14 pulses of PRL secretion per day occur in healthy men with an average inter-pulse interval of 95 min (Nokin et al. 1972). Thus, the time of blood sampling has to be considered when determining PRL responses to exercise. Furthermore, environmental inputs, internal milieu, and the reproductive state can modify the circadian pattern of PRL (Freeman et al. 2000) and therefore might modify the exercise-induced hormonal responses.

Basal PRL levels and responses to PRL releasing stimuli, such as exercise, are higher in women than men. PRL levels are basically unchanged throughout the menstrual cycle with only a slight increase in PRL during the luteal phase (Fujimoto et al. 1990). PRL responses to exercise, however, are greater in the mid-luteal phase than in the early follicular phase of the menstrual cycle. Abundant evidence is available to suggest that basal PRL concentration and PRL release during exercise and following maximal and submaximal exercise are reduced in runners with amenorrhea despite high lactate levels (De Souza et al. 1991). Similar to pregnancy, a blunted response to 10 min moderate exercise has been recently reported (Rojas Vega et al. 2012). In this study it was shown that despite the fact that the ability to perform strenuous exercise during pregnancy is not reduced, the achieved maternal lactate concentrations were low during exercise. Thus, one possible explanation for this apparent inconsistent response of PRL may be that when exercise is of short duration only acidosis induces PRL augmentations in humans.

An accumulation of H^+, produced by an increase in lactate concentration, glucose availability, and oxygen availability have been suggested as PRFs during exercise. At high exercise intensities the anaerobic lactic contribution seems to be an important trigger for inducing PRL augmentation (De Meirleir et al. 1985a). The underlying mechanism might be mediated by 5-HT, since this neurotransmitter plays a crucial role in central chemosensitivity (Rojas Vega et al. 2006b). Extensive evidence is available which shows that serotonergic neurons are central carbon dioxide sensors in maintaining pH homeostasis (Richerson 2004), and the primary serotonergic response to hypercapnia acidosis consists of an activation of the respiratory function aimed at restoring pH value to normal. Studies showing that hypercapnia acidosis causes an augmentation of PRL secretion in humans at rest (subjects inhaled 6 L of a gas mixture comprising 7% by volume carbon dioxide and 93% by volume of oxygen in 4 min from a respiration bag through a face mask) support the hypothesis that a chemosensitivity-related 5-HT system activation disturbs the hypothalamo-pituitary PIF-PRF balance, causing acute PRL secretion (Rojas Vega et al. 2003). In support of an acidosis etiology, buffering of metabolic acidosis during intensive cycling to exhaustion, resulting in a reduced drop of pH, has also been reported to reduce the increase of plasma PRL levels in humans (Rojas Vega et al. 2006b).

It is known that environmental stimuli such as thermal stress or oxygen availability can affect the PIF-PRF hypothalamic regulatory mechanisms modifying PRL secretion (Freeman et al. 2000; Strüder et al. 1996). Such modifications must be taken into account for interpretations of data obtained from exercise trials. For example, during exercise PRL levels were reported to increase during oxygen breathing (Strüder et al. 1996). In addition, an inhibition of exercise-induced increase of PRL levels was observed in males during GXT, who had been acutely exposed to hypoxia (Bouissou et al. 1987).

It is not yet clear how these increases of PRL affect the brain, but it is conceivable that they are linked to neurogenic processes. Augmented PRL levels during exercise might be important for boosting neurogenesis. This hypothesis is also based on the finding that the missing action of the hormone in PRL-receptor-deficient mice leads to a reduction of neurogenesis (Shingo et al. 2003). Combined with the findings that neurogenesis is augmented during conditions that increase PRL concentration, like pregnancy or after peripheral or central infusion of the hormone (Shingo et al. 2003), it may be argued that PRL plays a functional role in brain neuroplasticity, giving further support to the assumption that exercise may be beneficial for the brain.

8.4 Amino Acids and Neurotransmitters

5-HT and dopamine (DA) are neurotransmitters which have an important functional role during exercise in humans. An augmentation of the DA activity by administration of the DA agonist pergolid-mesylat was shown to reduce systolic blood pressure, pulse rate, and lactate level during GXT (De Meirleir et al. 1987). The maximal performance capacity was increased while the typical exercise-induced augmentations of PRL and ACTH were suppressed. During cycle ergometer exercise, 5-HT antagonism by the application of ketanserin induced a reduction of systolic blood pressure. The maximal performance capacity remained unchanged, while the lactate curve shifted to the right, which is an expression of either reduced lactate production in the working muscle cells or increased lactate elimination. Ketanserin also reduced the concentration of exercise-induced rise of ACTH, while the growth hormone (GH) concentration was not altered (De Meirleir et al. 1985b). Administration of the 5-HT reuptake inhibitor paroxetin reduced performance capacity to fatigue during continuous exercise, however, did not affect the exercise-induced PRL release (Strüder et al. 1998a) (Fig. 8.3).

Interestingly, a co-release between the BDNF and 5-HT has been demonstrated (Mattson et al. 2004). 5-HT regulates the most extensive modulatory behavioral system in the human brain. 5-HT projections are influenced by extrinsic and intrinsic impulses from different cortical brain areas, which reach Raphe nuclei over feedback loops and contain external and internal body information about planning, evaluation, motivation, or excitation (Graeff 1997). Although central serotonergic neurotransmission during exercise is predominantly regulated by neuronal complex

cooperation in the brain, precursor supply and plasma concentrations, fixation of TRP to albumin, hepatic and non-hepatic TRP pyrrolase, as well as competitive TRP uptake at the BBB are peripheral mechanisms that also influence central 5-HT neurotransmission. Motor neuron functions are primarily enhanced by the function of the serotonergic neurons in the brain, but also by the influence of central 5-HT and to a certain extent the neurons in the spinal cord.

The TRP stimulation of TRP hydroxylase is important for the central 5-HT impact, since this key enzyme is unsaturated. TRP uptake can also be aided by adrenoceptor-dependent dilatation of the microvessels or metabolically by an increased efflux of glutamine from the brain after central ammonia (NH_3) increases—e.g., during strenuous physical work (Mans et al. 1983). Exercise-dependent activation not only includes motoric neuronal activity, but also the release and reuptake of 5-HT and DA at presynaptic neuronal axons and somato-dendritic secretion. During the exercise detachment of TRP from albumin, TRP uptake at the BBB and TRP hydroxylase activity is increased, together with a higher TRP enzyme saturation and larger 5-HT yield. During exercise this is supported by faster anterograde TRP hydroxylase transport from cell body to axon terminal by neuron excitation, in which the 5-HT biosynthesis has increased. CA^{2+}-dependent 5-HT release into the synaptic cleft augments and postsynaptic 5-HT receptor subtype stimulation is enhanced.

But there are situations in which this well-balanced equilibration is disturbed and a dysfunction of the 5-HT system occurs. This might be induced by a non-physiological increase of free TRP liberation by adrenergic FFA mobilization with a consequent rise in their blood values after exercise, fasting, or emotional adrenergic exertion due to lipolysis in adipose tissue (McMenamy 1965). This might be the case during long-lasting strenuous exercise without ergogenic aid. In combination with augmented BCAA metabolism, an increase of the free TRP/BCAA ratio will occur, which favors free TRP uptake at the BBB and the resulting enhancement of 5-HT biosynthesis. Peripheral TRP concentration can be reduced by activation of the hepatic TRP pyrrolase. In addition, an increase in extrahepatic pyrrolase activity caused by γ-interferon diminishes plasma TRP concentration while simultaneously reducing viral and bacterial susceptibility (Strüder and Weicker 2001).

The 5-HT system adjusts impulses for behavior and mood modulation, but also supports complex cognitive or neuromuscular functions (Baumgarten and Grozdnovic 1995). Raphe nuclei are pacemakers of 5-HT central propagation, which control 5-HT projections by collaterals and receptor activation of many brain areas. Raphe nuclei receive information of behavioral modulation from diverse cortical regions. These impulses are already integrated in the Raphe nuclei before ascending and descending impulses arise. This equilibrating key function of the 5-HT system is essential in order to adjust neuro- and behavior modulation by coordination of different neurotransmitters, which are prerequisites for efficient neuronal networks. It seems that the adjustment of central neuro-modulation by 5-HT compensates central stress-induced dysregulation. Dysfunctions of the 5-HT system, however, are more obvious than the well-adjusted physiological implication of the 5-HT system, and this might be the reason for the underestimated beneficial impact of 5-HT in exercise-related studies.

8.5 Concluding Remarks

A large number of studies with differing methods of approach to the influence of physical exercise on the brain and cognitive factors are currently available. It may be concluded that the knowledge of the biochemical and biophysical connections between the functioning of the brain, mind, and body during physical exercise is important in preventive and therapeutic approaches. Exercise improves overall CNS health by augmenting neurotrophic factors and hormones as well as by affecting the neurotransmitter systems. Thus, from a clinical point of view, exercise is an ideal strategic tool for inducing anxiolytic and antidepressant effects, for enhancing cognition and facilitating functional recovery after injury (i.e., stroke) and through its influence on neurogenesis. Future studies should strive to establish a more precise dose–response relationship between exercise, humoral factors, and neurogenesis in humans, thereby allowing exercise's possible contribution to health to be optimized via prevention and also rehabilitation programs.

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