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Blood-Brain Barrier and Exercise – a Short Review

by

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Blood-brain barier (BBB) segregates central nervous system (CNS) from the circulating blood. BBB is formed by the brain capillary endothelial cells with complex tight junctions between them as well as by astrocytes and pericytes. BBB is responsible for transport of selected chemicals into and out of the CNS as well as for its protection from fluctuations in plasma composition following meals, during exercise and from circulating agents such as neurotransmitters, xenobiotics and other potentially harmful substances capable to disturb neural function. BBB may be compromised during CNS injury, infection, fever and in some nerodegenerative diseases. The increase of BBB permeability was observed also during exercise as documented by changes of plasma S-100 protein levels, used as a peripheral marker of BBB integrity. Marked change in BBB integrity during exercise may disturb normal brain function and contribute to the development of central fatigue. Moreover, serum S-100β may indicate level of injury in individuals suffering brain injuries during sports. There are also data suggesting that acute effect of physical exercise on serum S100β levels may not be related with CNS injury. Further studies to establish whether training and which type of it may modulate BBB permeability are needed.

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The blood-brain barrier (BBB) is a semipermeable membrane that regulates the transport of selected chemicals into and out of the central nervous system (CNS). It is formed by complex tight junctions between brain capillary endothelial cells and segregates the circulating blood from interstitial space in the brain (Ballabh et al. 2004, Sendrowski et al. 2004). The BBB protects the brain from fluctuations in plasma composition following meals and during exercise, and protects against circulating neurotransmitters, xenobiotics and other potentially harmful substances that could disturb neural function (Abbott 1998, 2002, 2005). Small lipophilic molecules such as oxygen or CO_2, which is known to be elevated during exercise, can freely diffuse across the BBB (Abbott 2002, Ballabh et al. 2004). Small polar solutes needed for brain function are transported by a number of specific carriers located within the BBB. In recent years, GLUT-1 for glucose transport, L-system carrier (L1) for large neutral amino acid transport, and specific carriers mediating the efflux of potentially toxic metabolites (e.g., glutamate) from the CNS have been documented in the BBB (Abbott 2002). The brain endothelium is capable of endocytosis/transcytosis, although to a lesser extent than peripheral capillaries. However, it possesses specific systems for receptor-mediated and adsorptive endocytosis that can transfer peptides and lipoproteins into the brain (Abbott 2004, 2005, Ballabh et al. 2004). The brain endothelium contains a number of enzymes supporting the protective and detoxifying functions of the BBB, including monoamine oxidase; these enzymes ensure that central synaptic function is not affected by circulating neuroactive agents (Abbott 2002, Ballabh et al. 2004). This system has been postulated to protect against elevation of catecholamines within the brain in response to elevated plasma catecholamine concentrations during exercise. Thus, the term BBB covers a number of static and dynamic properties that enable the endothelium to protect and regulate the brain microenvironment (Abbott 1998, 2002, 2005, Ballabh et al. 2004). While the BBB is largely resistant to changes in permeability, there are situations where the function of the BBB may be compromised, including neuronal damage, infection, fever and some neurodegenerative diseases. Recently, widespread increases in BBB permeability have been observed during exercise. These changes were found by measurement of plasma and cerebrospinal fluid (CSF) S-100 protein levels. S-100 serves as a peripheral marker of BBB integrity and is quite frequently considered a marker of CNS damage (Kapural et al. 2002, Sendrowski et al. 2004, Himeda et al. 2006).

It is not known whether BBB transport of given compounds can be modified during exercise without noticeable changes in BBB permeability. Evidence for marked lactate uptake by the brain has been revealed by determination of a-v differences and the cerebral metabolic ratio defined as O_2/glucose + 1/2 lactate

during exercise of moderate intensity (Ide et al. 1999, Dalsgaard et al 2004). When exercise intensity is mild to moderate, the muscle tissue is exercised without marked changes in the membrane permeability as indicated by a lack of change in plasma creatine kinase activity (Brancaccio et al. 2007). These studies showed that low to moderate exercise intensities do not damage cells and probably does not affect BBB permeability. Moreover, free tryptophan transport through the BBB is elevated in response to exercise-induced plasma FFA enhancement; this causes so-called central fatigue (Davis and Bailey 1997, Chalimoniuk et al. 2005). Since this effect was partially inhibited by branched-chain amino acid supplementation prior to exercise, it is obvious that BBB permeability was unchanged under these experimental conditions (Yamamoto and Newsholme 2000).

Role of astrocytes in BBB integrity during exercise

Astrocytes play a major role in neuronal metabolism, nutrition and recycling of used substrates. Astrocytes that connect to pial matter have the abilities of transcytosis and active ion transport. Astrocytes mediate transfer of substances from the cardiovascular system to neurons (Magistretii 2006). Physical exercise can induce astroglial proliferation in the frontoparietal cortex and dorsolateral striatum in association with extensive angiogenesis (Li et al. 2005). Li et al. (2005) suggest that astrocytosis after exercise coupled with angiogenesis may strengthen the neurovascular unit (a structure consisting of microvascular endothelium, astroglia, neurons and the extracellular matrix). Strengthening of this unit by exercise may protect the blood-brain barrier from disruption following brain injury or after stroke (Li et al. 2005).

S100 β protein as a marker of brain damage

S100 is a calcium-binding peptide produced by reactive astrocytes and observed mainly in the cytoplasm of astrocytes (Muramatsu et al. 2003) and Schwann cells (Isobe et al. 1984). The function of S-100 in the central nervous system (CNS) is only poorly understood. It is known that S-100 plays a role in neuronal plasticity and long-term potentiation processes (Kiełbińska and Sołtys 2008). This protein is expressed at high levels in the brain and is known to be a marker of brain damage. Several reports suggested that the over-expression of S100β protein might exacerbate neurodegenerative diseases such as Down syndrome, Alzheimer's disease, and Parkinson's disease (Griffin et al. 1989, Sheng 1997, Himeda et al. 2006). Overexpression of S100◎ protein by reactive astrocytes may play a key role in the pathogenesis of neuronal damage after transient cerebral ischemia (Muramatsu et al. 2004). Muramatsu et al. (2003) re-

ported that expression of S100β protein was related to neuronal damage in an MPTP-induced model of parkinsonism in mice.

An interesting recent study reported that enhanced synthesis of 100β protein by reactive astrocytes was associated with inflammatory responses within the peri-infarct area; this may be related to the occurrence of delayed infarct expansion during prolonged focal ischemia (Matsui et al. 2002). In contrast, Migheli et al. (1999) suggested that S100β expression was unrelated to neuronal apoptosis, but might be involved in a cellular defense mechanism against oxidative stress. Importantly, it is generally believed that S-100◎ does not cross the BBB in normal physiological conditions.

S100 β level in serum as an indicator of BBB permeability

Levels of S100◎ in plasma are typically extremely low, at only one third of the levels observed in the cerebrospinal fluid (CSF) (Sendrowski et al. 2004). An elevated level of S-100 in the CSF is generally considered to be a marker of nervous tissue damage. The presence of this protein in blood serum indicates functional and/or morphological disruption of the blood-brain barrier (Kapural et al. 2002, Sednarowski et al. 2004). This protein is generally considered to be a marker of CNS damage (Kapural et al. 2002, Sendrowski et al. 2004). Increased levels of S-100 in CSF or serum were found after a variety of cerebral lesions and injuries including stroke, severe head trauma, brain tumors, or multiple sclerosis (Isobe et al. 1984, Marchi et al. 2003, Sendrowski et al. 2004). Thus, opening the blood-brain barrier (BBB) would be expected to markedly increase plasma S-100 levels. Kapural et al. (2002) suggest that S-100◎β is an early marker of BBB disruption that is not necessarily related to neuronal damage (Kapural et al. 2002).

Changes in S-100β level during exercise

Watson et al. (2006) examined changes in serum S100β concentrations in response to exercise under hot conditions with and without fluid ingestion. That study found that water ingestion could limit exercise-induced increases in serum S100β, consistent with the preservation of BBB integrity. It is possible that this response was mediated via maintenance of reduced extracellular osmolality in the later portion of the exercise period, thus limiting the osmotic movement of fluid across the BBB (Watson et al. 2005, 2006). The serum S-100β concentration has also been found to be elevated after prolonged exercise in warm environments, suggesting that BBB permeability may be altered. Animal studies have indicated a marked increase in BBB permeability after a forced swimming exercise (Dietrich et al. 2003). The development of hypertermia, increased sero-

tonergic activity, elevated circulating ammonia and epinephrine levels and increased production of proinflammatory cytokines may contribute to this response. These findings have two important implications: 1) altered BBB integrity during exercise may disturb normal brain function and contribute to the development of central fatigue; and 2) serum S-100β is now employed as an index of brain trauma in individuals who suffer brain injuries during sports. Changes in the permeability of the BBB to this protein may give misleading results in exercising individuals, particularly under conditions that lead to significant heat stress (Watson et al. 2005).

Recently, it was reported that patients presenting elevated serum levels S-100β after minor head injuries were more prone to develop neuropsychological deficits than those with lower levels of S-100β protein. Concentrations of this protein were assessed before and after amateur boxing competitions and sparring bouts. Serum level was also investigated in several control groups, including before and after a 25 km race, jogging (10 km), short-term running, and heading in football. S-100β protein levels increased after boxing and running, but not after ergometer cycling or soft heading of footballs. Increases in S-100β protein concentrations after competitive boxing and a 25 km race were significantly higher than with other activities. There was no significant difference between the effects of sparring and running. The number and severity of strikes to the head correlated significantly with increased S-100β protein levels (Otto et al. 2000). Increased S100β levels after a 7600 meter swimming race as compared to baseline values suggests an acute influence of physical exercise on serum S100β levels that is not related to CNS injury. Moreover, physical activity on a running wheel induces increased blood vessel density in brain (Abbott 2005, Ding et al. 2005, Gloor et al. 2001, Karen et al. 2002) and daily forced exercise on a treadmill also induces cortical and striatal angiogenesis (Broadwell et al. 1990, Ballabh et al. 2004, Brawn et al. 2003, Chaudhuri 2000). Such angiogenesis may be necessary to satisfy the brain's increased demand for oxygen and glucose (Li et al. 2005, Kobayashi et al. 1985).

Inflammatory mediators, BBB and exercise

Inflammatory mediators are known modulators of BBB permeability. Exercise shares many similarities with the acute phase observed during inflammatory diseases. Recently, elevated serum levels of S100A8 and S100A9, novel proinflammatory molecules of the S100 protein family, have been associated with various inflammatory diseases (Mopren et al. 2006). That study was conducted to assess the potential use of these molecules as inflammatory markers for the exercise-induced immune response. Seventeen male subjects with different

levels of training performed a marathon run. Furthermore, 13 subjects (10 male, 3 female) performed three different treadmill tests: strenuous, moderate, and downhill. S100A8/A9 complexes were measured by ELISA, while white blood cell count (WBC) and C-reactive protein (CRP) were used as markers of the inflammatory response. Serum creatine kinase (CK) concentration was determined as a marker for muscle damage. After a marathon run, S100A8/A9 levels increased dramatically during the early post-exercise period and returned to resting levels one day after the run. A similar pattern was found for WBC, while CK and CRP reached their maximum on the day after the run. Moreover, S100A8/A9 release was higher in the subgroup of well-trained athletes. The kinetics of S100A8/A9 release were prolonged after intense exercise. In summary, these results indicate that the novel pro-inflammatory molecules S100A8/A9 are very early and sensitive markers of the exercise-induced inflammatory response. Further investigations are necessary to evaluate the applicability of S100A8/A9 for monitoring the training process and to elucidate the dependence of S100A8/A9 levels on training status (Mooren et al. 2006).

Perspectives

The BBB maintains brain homeostasis by restricting the movement of molecules based on size, charge, hydrogen potential, and lipid solubility. Whereas many compounds penetrate the BBB by passive diffusion, many other agents undergo active influx or efflux using transport proteins. It has been recently postulated these processes are all affected by exercise-induced BBB damage. Thus, further studies should address the relationship of exercise mode, intensity and duration to BBB permeability. Further studies are also needed to firmly establish whether the training process might modulate BBB permeability. Since GLUT 1 and MCT1 play a crucial role in substrate delivery to the brain, it is necessary to investigate whether training causes adaptive changes in the numbers and activities of these transporters.

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