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Review Article

Measurements in the Blood of BDNF for RA Patients and in Response to Anti-TNF Treatment Help Us to Clarify the Magnitude of Centrally Related Pain and to Explain the Relief of This Pain upon Treatment

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Brain-derived neurotrophic factor (BDNF) is a neurotrophin with functions related to neuronal survival/proliferation processes and inflammation. BDNF is also an important central pain mediator. The levels of BDNF have been found to be high for RA patients with severe disease and to become lowered in response to anti-TNF treatment. New information says that the levels of BDNF in the blood parallel the BDNF concentrations in the brain and that BDNF can pass the blood-brain barrier. Furthermore, most of the circulating BDNF is produced in the brain. Habitual and regular exercise, in contrast to temporary exercise, does also lead to a lowering of BDNF blood levels. Both anti-TNF treatment and habitual and regular exercise do have pain-relieving effects. It might be that the pain-relieving effect of anti-TNF treatment is related to an affection of central neuronal regions, hereby influencing BDNF production. Measurements of BDNF in the blood help us to clarify the magnitude of centrally related pain for RA patients and help us to explain the relief of this pain in response to anti-TNF treatment.

1. Background

Measurements of factors in blood are regularly being undertaken for patients with rheumatoid arthritis (RA). Then comes the interpretation of the significance of the values obtained. One factor for which the levels were found to be higher for patients with severe RA than for controls, and for which the levels were found to be decreased in response to anti-TNF treatment, is the neurotrophin brain derived neurotrophic factor (BDNF) [1]. The significance of this observation has been unclear. However, based on the fact that BDNF is a central pain mediator and based on information obtained during the last 2 years concerning the interrelationship between the blood levels of BDNF and the concentrations of BDNF in the brain a new understanding is under way. An understanding that most of the circulating

BDNF originates in the brain is also of importance. The new information obtained can help us to better understand the BDNF blood levels in relation to marked pain for patients with severe RA and the pain-relieving effect of anti-TNF treatment.

2. General Aspects on Neurotrophins

Neurotrophins constitute a class of growth factors comprised by nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4) [2]. The most frequently studied neurotrophins are NGF and BDNF. The neurotrophins are initially synthesized as proneurotrophins that later are cleaved to their mature forms. They bind to two types of receptors, the high-affinity tyrosine kinase receptors (TrkA, TrkB, and TrkC) and the

low-affinity neurotrophin receptor p75 (NGFR-p75). The high affinity receptors bind the neurotrophins with different affinity, NGF binding to TrkA, BDNF and NT-4/5 binding to TrkB, and NT-3 binding to TrkC, whilst the low-affinity receptor NGFR-p75 binds all neurotrophins with similar affinity [3–5].

Synthesis of neurotrophins occurs particularly in neurons and inflammatory cells, and also in other cell types. That includes keratinocytes, epithelial cells and cells within the connective tissue and skeletal muscle [6]. A cell type recently observed to show expression of neurotrophins is the tenocyte of Achilles tendons [7].

3. Functional Aspects for Neurotrophins

The neurotrophins promote the survival of neurons [8, 9] and are important for cell proliferation [10] and inflammatory processes [11]. Following nerve injury, there is an upregulation of neurotrophin expression [12]. There is often an overexpression of neurotrophins during inflammation processes [11], and neurotrophin receptors are, for example, overexpressed in human airways infected with respiratory syncytial virus [13]. In studies on ulcerative colitis, it was found that there was an upregulation concerning neurotrophins for the lamina propria cells, these mainly conforming to inflammatory cells, whilst there was a downregulation in expression for these in the nerve structures [14].

Observations made in studies on the development of insulinitis for the nonobese diabetic (NOD) mouse, a model for type 1 diabetes, suggested that there are attempts by neurotrophins to promote nerve ingrowth and survival of the pancreatic islets in this situation [15]. It is argued that the increased expressions of neurotrophins that occur in brain lesions [16] and gut inflammation [17] are related to neuroprotective roles. Overexpressions of neurotrophins may actually be involved in the modulation rather than the induction of inflammatory responses [18]. The neurotrophins can on the whole fulfill a link between the nervous and immune systems.

Neurotrophins do also have apoptosis-modifying functions [19]. Neurotrophins can have an importance in relation to pain sensations as well [20], including the pain that is associated with inflammation [21].

4. Focus on BDNF in the Present Review

Focus is in the present paper directed towards BDNF. Recent data obtained do, as described above, thus favour that it is indeed of relevance to focus on BDNF concerning RA. BDNF has been considered to have a role as a major contributor to inflammatory pain and to on the whole be a central pain modulator [22]. BDNF has actions at central synapses in pain pathways [20] and is upregulated in the dorsal horn following peripheral inflammation [23]. It is suggested that the BDNF/TrkB system may for example contribute to persistent pain after tooth repair [24]. Interesting observations on the interplay between the brain and peripheral blood BDNF concentrations have been documented in recent studies.

5. Importance of BDNF for Joints, Including in Arthritis

It has long been argued that neurotrophins may be involved in arthritic processes [25, 26]. That was primarily suggested to be the fact for NGF. Evidence which favoured such a suggestion were the findings of increased levels of NGF in synovial fluid [25, 27] and peripheral blood [28, 29] for patients with chronic arthritis, spondylarthropathy, and RA. An upregulation of NGF in mononuclear cells infiltrating the inflamed synovium and an increase in synovial nerve fibers expressing NGFR-p75 were also noted in studies on the rat [30]. Evidence which suggested that NGF might have a role in the healing phase of joint inflammation was also presented [18].

More recently, research has been performed concerning BDNF and human synovium and arthritis. The existing information says that BDNF is produced locally in synovial tissue, that BDNF mRNA can be detected in the inflammatory synovium of RA patients [31] and that there are BDNF immunoreactions for macrophages and fibroblasts in the human synovial tissue [32]. There is BDNF expression in neurons supplying the synovial tissue as well, and immunoreactions for both NGFR-p75 and TrkB, to which receptors BDNF bind, occur for nerve fascicles and for strands located within lymphoid aggregates in the human synovial tissue [1]. NGFR-p75 reactions are also present in association with the blood vessels [1]. As both TrkB and NGFR-p75 immunoreactions are detectable in the human synovial tissue, it is presumable that BDNF has local effects via having interactions with these receptors. An important function for BDNF locally in the synovial tissue may not least be related to influences on the nerve structures. Such a suggestion is in line with the known fact that neurotrophins, as discussed above, show survival-promoting, healing, and protective effects for neurons.

In studies on a mouse model of arthritis that is similar to the collagen-induced arthritis model, namely, local injection-induced arthritis [33], marked expressions for NGF and BDNF, as well as their receptors, could be seen in the inflammatory infiltrates of the arthritis animals [34]. Expressions of NGF/BDNF and the neurotrophin receptors were also seen in the articular chondrocytes lining the joint cavities. However, reduced neurotrophin receptor immunoreactions in chondrocytes were seen for severely arthritic animals [34]. Expressions of NGFR-p75 and TrkA, as well as NGF, have also been noted for human articular chondrocytes [35, 36]. The findings concerning the lining cartilage in the mouse model suggest that neurotrophins are of importance for the cartilage lining the joint cavity having autocrine/paracrine effects and that the decrease in expression levels of the neurotrophin receptors seen in severe arthritis can be a drawback for cartilage function.

BDNF has been found to be measurable in the synovial fluid in only a subpopulation of RA patients [1, 32]. It is thus possible that leakage of BDNF into the synovial fluid only occurs to a small extent for RA patients and that BDNF mainly becomes bound to its receptors in the synovium or

the lining cartilage instead of being released into the synovial fluid.

6. BDNF Can Be Analysed in Blood

BDNF can be measured in plasma as well as in serum. Interesting observations have been made in this regard during recent years. This means that it has been found worthwhile to analyse for BDNF blood levels.

The blood levels of BDNF have been found to be elevated in several conditions, however, not all. There are increased blood levels of BDNF in patients with fibromyalgia [37, 38] and atopic dermatitis [39]. The blood levels of BDNF are also found to be significantly higher during a migraine attack than in pain-free periods [40]. Patients with multiple sclerosis show higher BDNF levels in the blood than healthy controls [41]. On the other hand, the BDNF levels in the blood were found to be lower for patients with early stage glaucoma than for control subjects [42].

It is frequently documented that the serum levels of BDNF are decreased in major depressive disorders [43, 44]. There is also evidence which favours that BDNF may actually play an important role in the pathogenesis of these disorders [45] and that BDNF signaling may also contribute to the pathogenesis of schizophrenia [46]. Adults with epilepsy are reported to have decreased levels of serum BDNF [47].

7. BDNF Blood Levels in Relation to Severity of Diseases

A relationship between disease severity and BDNF levels has been noted for certain situations. There is a lowering of the BDNF plasma levels with increasing severity of depression in patients with mood disorders [48]; that is, there is a negative correlation between BDNF blood levels and the severity of depression [43]. An increase in BDNF levels has been seen for psychotic patients that have been treated with the antipsychotic olanzapine but not other tested antipsychotics [49]. The serum BDNF level is reported to be a biological marker for the severity of psychiatric symptoms in patients with neuropsychiatric systemic lupus erythematosus [50].

It is described that there is a relationship between serum BDNF levels, but not serum NGF levels, and disease severity in atopic dermatitis [51]. It has also been shown that subjects with moderate or severe asthma have higher BDNF levels in plasma than patients with mild asthma and controls [52]. Müller and collaborators [52] suggest that BDNF might be a potential biomarker for clinical severity for children with asthma.

It has been shown that plasma BDNF significantly correlates with multiple risk factors for metabolic syndrome and cardiovascular function [53]. Accordingly, increased levels of cardiorespiratory fitness and habitual exercise are associated with lower resting levels of serum BDNF levels in healthy humans [54]. Also, in another study, it was considered that the BDNF blood levels correlate with risk factors for metabolic syndrome [55].

8. Influence of Physical Activity on Brain and Peripheral Blood BDNF

Physical exercise enhances the mood and cognitive functions, increases the expression of BDNF in the brain and can short-term increase plasma and serum BDNF concentrations in humans [56]. Knaepen and collaborators [57] have written a comprehensive review concerning the aspects of exercise-induced responses of BDNF. It was concluded that in the majority of studies performed, there was a transient increase in plasma or serum BDNF concentration following an acute aerobic exercise. Resistance exercise induces a robust but transient elevation of circulating BDNF [58]. That includes the situation for persons with major depression [59]. Exercise is shown to have effects in the brain via activation of the BDNF-TrkB signaling pathway [60].

However, it is important to note that the situation is different for persons who experience habitual exercise, than those who train irregularly. Recreational male runners have thus lower serum levels of BDNF than matched control individuals [61], indicating a downregulation of BDNF with marked habitual exercise. Also the study by Currie and collaborators [54] show this fact (c.f. above).

9. Comparisons between Brain and Peripheral Blood BDNF Levels

It has recently been shown that measures of serum and plasma BDNF levels reflect brain-tissue levels across species [62]. It is also shown that in parallel with the occurrence of an increased BDNF expression in the hippocampus in response to endurance training, there is an enhanced release into the blood from the brain [63]. It is obvious that BDNF can cross the blood-brain barrier [64], there being a release of BDNF from the brain to the blood [65]. BDNF in the blood can also be retrogradely transported to the brain, hereby crossing the blood-brain barrier.

The circulating BDNF is known to originate both from the brain and from peripheral sources. It is considered that the brain constitutes almost 75% of the circulating BDNF [65]. The peripheral sources are constituted by a large number of cell types [57].

10. BDNF in Blood in Response to Anti-TNF Treatment for RA Patients

In studies on the blood levels (plasma) of BDNF, the effects of a TNF-blocker (infliximab) were examined in our laboratory [1]. Plasma of 18 patients with RA who had failed on disease modifying antirheumatic drugs were examined. Infliximab (3 mg/kg body weight) was given as intravenous infusion according to recommendations, at baseline, and at 2 weeks, 6 weeks, and thereafter every 8 weeks. Seventeen of the patients had also been treated with methorexate. It was found that the BDNF level before the anti-TNF treatment was 4 600 pg/ml (median) and (Q1–Q3) 3 700 to 7 600 pg/ml. There was a trend towards a decrease after 2 h after the initial treatment. At examination 14 weeks after starting treatment,

the levels of BDNF had decreased significantly. There was no significant difference between the levels of BDNF found for 14 weeks samples and 30 weeks samples. The baseline level was higher than that for healthy controls.

The finding that anti-TNF treatment leads to a decrease in BDNF levels is partly in line with observations made in a previous preliminary report [66]. In that study, it was described that the plasma levels of BDNF decreased, but not significantly, in response to this treatment. It is obvious that anti-TNF treatment can have an influence on the BDNF levels. This is an interesting aspect and an aspect that has not previously been considered when discussing the effects of this treatment.

11. Interplay between BDNF and TNFalpha; Relation to Pain

It has previously been noted that TNFalpha enhances the secretion of BDNF from circulating human monocytes [67]. However, it is not obvious that anti-TNF treatment has its effect on inflammatory related BDNF. The levels of BDNF in plasma after anti-TNF treatment thus did not correlate with inflammatory parameters, nor were there any correlations between levels of BDNF in synovial tissue and the number of inflammatory cells observed microscopically [1].

Based on our findings of BDNF/TrkB immunoreactions in nerve structures in the synovial tissue, recent findings of interrelationships between TNFalpha/BDNF-BDNF receptors for nerve structures are noteworthy. In studies using a rat model of herniated nucleus pulposus in relation to spinal cord damage, it has thus been shown that infliximab appears to prevent hyperalgesia [68] and that this treatment attenuates the BDNF levels in the dorsal root ganglion and spinal cord [69].

Based on the new information described above, it is obvious that the blood levels of BDNF correlate with the brain levels of this neurotrophin, that BDNF passes the blood-brain barrier, and that as much as 75% of the BDNF is actually originating from the brain. It is also obvious that there is a similarity between the effects that anti-TNF treatment and habitual and regular exercise have on blood levels of BDNF, the levels becoming decreased in both cases. That should mean that the brain levels are lowered as well. So, it can be hypothesized that the pain relief that the anti-TNF treatment has can be related to a downregulation of BDNF brain (and secondarily blood) levels. BDNF is, as commented on above, recognized as an important central pain mediator. A lowering of brain BDNF levels should therefore be a favourable situation. It is a well-known fact that regular physical activity and exercise, if it can be performed, can have pain-relieving effects for persons with RA.

It should here be recalled that it has long been asked how anti-TNF treatment achieves the rapid pain relief that can occur. A new study favouring that neutralization of TNFalpha indeed has effects on nociceptive brain activity is therefore very interesting. Via the use of functional MRI, it was thus shown that nociceptive CNS activity in several brain regions were blocked after infusion of a monoclonal

antibody to TNFalpha at early time points, that is, at time points at which joint swelling and acute phase reactants were not affected [70].

12. Concluding Remarks

The existing information says that:

- (1) BDNF levels can easily be analysed in both plasma and serum.
- (2) The blood levels of BDNF in patients with severe RA are elevated as compared to controls and these levels are decreased in response to anti-TNF treatment.
- (3) BDNF is an important factor to analyse for in RA as it is related to pain symptoms and as the BDNF/TrkB system is likely to be of significant importance for the inflammation and the nerve structures in the synovium and for the lining cartilage of joints. Even more important is the fact that BDNF is a central pain mediator.
- (4) There are correlations between brain and blood BDNF levels. Most of the BDNF we analyse in the blood comes from the brain.
- (5) The situation with a downregulation of the BDNF levels in response to anti-TNF treatment is comparable with the situation seen for persons exhibiting regular and habitual exercise. Temporary exercise leads instead short-term to an increased level of BDNF in the blood.
- (6) A new understanding of the relationship between BDNF and TNFalpha has been achieved. Measurements of BDNF in the blood can thus help us to clarify the magnitude of centrally related pain for RA patients and help us to explain the relief of this pain in response to anti-TNF treatment.

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