



The role of peripheral brain-derived neurotrophic factor in chronic osteoarthritic joint pain

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Brain-derived neurotrophic factor (BDNF) is a critical signaling protein in the human nervous system. It is found in high levels throughout the mammalian brain and spinal cord, as well as in the peripheral circulation (1-3). The multifaceted role of BDNF depends on the developmental stage of the nervous system. Previous research has demonstrated its role in initial development of the nervous system, synaptogenesis, and maintenance of existing neurons (4). Perhaps not surprisingly, therefore, BDNF has also been implicated in several studies to play a role in pathways related to pain perception. In their published work in this issue entitled “Peripheral brain-derived neurotrophic factor contributes to chronic osteoarthritis joint pain,” Gowler and colleagues highlight a heretofore uninvestigated role for BDNF in the modulation of pain related to osteoarthritis (OA) (5). This important study provides a potential mechanism behind OA pain and carries promise for future work into disease-modifying therapies to treat OA.

BDNF expression

Location of expression

BDNF's expression in many different human tissues contributes to its central role in nervous system regulation. Hofer and colleagues found during initial research that BDNF is expressed in all major regions of the human brain. However, the hippocampus and cerebral cortex were found to be the locations of highest expression of BDNF mRNA (1). BDNF mRNA was further sublocalized to the neocortex, piriform cortex, amygdala, hippocampus, claustrum, thalamus, hypothalamus, and brainstem (2). BDNF immunoreactivity was observed without mRNA expression in several brain regions, as well as the dorsal horn of the spinal cord. Microglia were also found to contain significant repositories of BDNF (6). Subsequent investigations found measurable levels of BDNF in circulating blood serum (3).

Method of expression

BDNF's multiplicity of roles in the nervous system may be in part facilitated by several differing protein products created during its synthesis. Similar to other neurotrophins, BDNF is first synthesized in the endoplasmic reticulum as a precursor molecule, pre-proBDNF. After cleavage of the signal sequence, proBDNF, a ~32-kDa polypeptide is formed. Pro-BDNF is then cleaved by proteases into a ~13-kDa mature BDNF (mBDNF) (7). Both proBDNF and mBDNF isoforms are subsequently released as signaling molecules from the cell (8,9).

Function of BDNF

As with the other neurotrophins, the different isoforms of BDNF bind preferentially to separate cellular receptors. mBDNF binds to the TrkB receptor, causing dimerization, autophosphorylation, and subsequent activation of the MAPK, PI3 kinase, and PLC- γ signaling pathways (10). The overall effect of this signal is a pro-survival effect and long-term potentiation in exposed neuronal populations. Conversely, proBDNF exerts its effects primarily through the p75 neurotrophin receptor (11). Interaction between proBDNF, p75, and a coreceptor named sortilin triggers several intracellular signaling cascades, including RhoA, which is responsible for neuronal growth cone and motility and NF- κ B, which is responsible for neuronal survival during development. However, the most notable action of proBDNF occurs through the JNK pathway, which ultimately leads to cellular apoptosis. Thus, proBDNF plays an important role in long-term depression, as well as neuronal development and remodeling (4,11).

The opposing effects of mBDNF and proBDNF have been described as a "yin-yang" system that controls synaptic plasticity (12). Indeed, the ratio of mBDNF to proBDNF has been shown to increase between the postnatal period and adulthood (13). Decreased levels of BDNF have been observed in Alzheimer's disease, and normal aging (14,15), while derangements in the ratio of mBDNF to proBDNF have also been observed in Alzheimer's disease and other neurodegenerative pathologies (14).

BDNF and pain

Perhaps unsurprisingly given its vital role throughout the nervous system, BDNF has also been implicated in chronic pain pathologies related to its ability to drive sensitization

of pain pathways. BDNF signaling has been shown to play a role in inflammatory pain via actions in sensory neurons. In this regard, BDNF-knockout mice were demonstrated to display attenuated inflammatory pain responses (16). In the period immediately following peripheral nerve injury, BDNF has been shown to mediate the transition between acute and chronic pain. Experiments where BDNF activity was attenuated via genetic knockdown demonstrated decreased development of allodynia and hyperalgesia in the post-injury period in BDNF-deficient subjects (6). This effect of BDNF can be seen in both the peripheral sensory neuron and the spinal cord, where BDNF is released by microglia (6). BDNF action to increase neuronal hyperexcitability and therefore pain perception in the spinal cord can be explained through both its activation of dorsal horn NMDA receptors and its attenuation of inhibitory GABA signaling by blocking action of the KCC2 potassium-chloride channel (17).

Centrally, BDNF has been implicated in chronic pain states through its effects on descending inhibitory pathways. Neurons in the periaqueductal gray have been shown to release BDNF in response to inflammatory insult, increasing sensitization to pain via NMDA receptor signaling (18). Peripheral serum levels of BDNF have been shown to rise in humans over the course of withdrawal from opioid drugs, perhaps indicating central resensitization to pain (19). Higher serum levels of BDNF are also correlated with lower amounts of descending modulation of pain pathways, as well as decreased tolerance to heat pain (20).

OA summary

OA is a common degenerative disease of joints. OA of the knee and hip has increased greatly in recent years due to the aging of the population and now represents the 11th-leading cause of disability worldwide. One analysis showed that OA costs could total up to 0.25% to 0.50% of a country's gross domestic product (GDP) (21).

The role of BDNF in this debilitating disease has been investigated in several studies to date. Comparison of knee OA patients versus healthy controls found that BDNF levels were significantly elevated in the serum of OA patients but were decreased in the synovial fluid compared to healthy controls. Serum BDNF levels were positively correlated with self-reported pain levels in OA patients (22).

Despite BDNF's putative role in the generation of OA joint pain, it has also been shown to correlate to the therapeutic response to exercise in OA patients. Analysis of

women with knee OA following a 12-week exercise program found increased serum levels of BDNF in tandem with increased functional status and decreased pain perception (23). A similar finding was reported in a randomized trial evaluating the efficacy of whole body vibration (WBV) therapy in women with knee OA. Women treated with WBV demonstrated increased BDNF levels as well as increased muscle strength, and there was a significant correlation between BDNF level and muscle strength (24).

Commentary

The recent work published by Gowler and colleagues further explores the relationship between BDNF expression and OA pain. The investigation tests this relationship in both human and animal models. Examination of synovium from human OA patients revealed the presence of BDNF and TrkB mRNA, and TrkB mRNA levels were significantly correlated with expression of the proinflammatory protein CX3CL1 (fractalkine). However, the researchers did not find a significant relationship between BDNF and CX3CL1 expression. In addition, there was not a significant difference in BDNF or TrkB expression between samples based on histologic classification as high- versus low-inflammation states.

A similar analysis was conducted in rats treated with monosodium iodoacetate (MIA), a known model for OA joint inflammation and pain. A multilevel model analysis revealed increased levels of TrkB in MIA-injected rats. ELISA indicated increased BDNF expression in these rats as well. In total, these results suggest an increased concentration of BDNF and TrkB in OA joints.

Armed with these results, the researchers subsequently investigated what role BDNF played in OA inflammation. Intraarticular injection of BDNF at 21 days post-MIA injection resulted in increased pain behavior [e.g., paw withdrawal threshold (PWT) or weight-bearing asymmetry] compared with MIA-injected rats treated with saline. Increased pain behavior manifested on average 5 days after BDNF injection and lasted until the end of the study period. Interestingly, the same BDNF injection in rats not treated with MIA did not result in increased pain behavior. BDNF pain sensitization in OA joints, therefore, seems to require an underlying OA pathology to be present and does not induce pain in healthy joints.

The effect of BDNF sequestration on OA joint pain was then investigated. A TrkB-Fc chimera selective for BDNF was injected into the affected joint. This injection significantly

decreased weight-bearing asymmetry in both chemical and surgical models of OA compared to a control IgG injection. PWTs were not significantly changed compared to controls. The authors then elegantly repeated the experiment in the contralateral knee. Injected TrkB-Fc failed to decrease pain behavior when injected into the contralateral joint from the OA model, thus demonstrating that the sequestration effects of TrkB-Fc are confined to the local environment. A final study was conducted to determine the length of action of the TrkB-Fc treatment. It was determined that no beneficial effects on pain behavior were seen starting at the 24-hour post-injection mark, thus suggesting the period of activity of TrkB-Fc is less than one day.

In this investigation, Gowler and colleagues have convincingly outlined a role for BDNF and its receptor TrkB in the mediation of OA joint pain. OA joints displayed higher levels of BDNF and TrkB, although it remains unclear the precise relationship between levels of these proteins and the degree of histologically observed joint degeneration in human subjects. Nevertheless, the crux of this investigation to the addition of previous literature is the demonstration of a BDNF-induced increase in pain behavior, which is then subsequently reversed by sequestration of BDNF via TrkB-Fc chimera. These results strongly suggest that BDNF is not elevated in OA joints merely as a side effect of joint pathology, but instead play a crucial causal role in the generation of pain during OA. BDNF injection was not able to cause a similar increase in pain activity in non-OA rats, implying that BDNF is a necessary but not sufficient component of OA joint pain. More generally, this investigation leaves the exact mechanism of BDNF-mediated joint pain in question. In this regard, further research must be conducted to determine how BDNF leads to increased pain in OA and if any other targetable steps in this pathway exist. However, this investigation represents a definite addition to the core of knowledge surrounding OA and proposes a strong first step towards developing novel therapeutics for OA pain.

The exact details of this posited therapy, sequestration of BDNF or blockade of signaling action, must be further investigated and refined, however. Unfortunately, the authors of this study determined that the action of TrkB-Fc in sequestering BDNF lasts at most 24 hours. Since this therapy is administered intraarticularly and does not seem to achieve systemic effects, daily TrkB-Fc injections seem like an impractical delivery method for this promising therapy. An effective anti-BDNF therapeutic option would have to achieve longer duration of action within the joint,

allowing for less frequent injections. Additionally, the potential adverse effects of blocking BDNF action must be considered in any therapy. As the authors mention in their discussion, previous therapies aimed at blocking a similar neurotrophin, nerve growth factor (NGF), while effective, also carried significant adverse effects. Tanezumab, an anti-NGF monoclonal antibody, was found to increase incidence of rapidly progressive OA (RPOA), especially in cases of high dosage, concomitant non-steroidal anti-inflammatory drug (NSAID) use, and pre-existing subchondral joint insufficiency (25). BDNF-blocking therapies may face a similar conundrum, especially given BDNF's role in maintaining neuronal structures throughout the rest of the body. Nevertheless, these results have suggested an exciting new avenue for potential treatments for OA pain. We eagerly await additional work that builds on Gowler and colleagues' fundamental findings in developing an end product that successfully improves quality of life for OA patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/apm-20-888>). The authors have no conflicts of interest to declare.

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