SciForschen
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ISSN 2379-7150

Journal of Neurology and Neurobiology

Editorial Volume: 4.1 Open Access

Lowering Pathologic TNF Levels Exclusively Within the Brain Rapidly Alleviates Long-Standing Injury-Induced Neural Pathologies

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Received date: 25 Oct 2017; **Accepted date:** 20 Nov 2017; **Published date:** 24 Nov 2017.

Citation: Spengler RN, Ignatowski TA (2017) Lowering Pathologic TNF Levels Exclusively Within the Brain Rapidly Alleviates Long-Standing Injury-Induced Neural Pathologies. J Neurol Neurobiol 4(1): doi http://dx.doi.org/10.16966/2379-7150.e111

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It is well known that injuries to the brain can result in a decreased quality of life, waning interactions with others, and overall patient disability, even to the point of not being able to perform one's daily living activities. Along with other pathologies, a primary component to traumatic brain injury (TBI) is chronic debilitating pain, termed neuropathic pain. This type of chronic pain is a poorly treated disorder related to long-term harmful cellular and behavioral changes, consequently requiring an innovative breakthrough therapy. Major therapy for acute and chronic pain is opioids. While opioids affect acute pain, their effect is limited and can be dangerous for chronic pain. In fact, the continued use of opioids for chronic pain has created a national emergency of opioid addiction and excess mortality, warranting a change in current therapy. Chronic neuropathic pain, as with numerous forms of injury, is associated with an inflammatory response. In particular, it is unchecked inflammatory responses that orchestrate the onset, development, and maintenance of chronic pain. Thus, chronic pain has a fundamental persistent inflammatory component that culminates in disabilities and impairment, as well as comorbid disease onset. Spread of inflammation along the neuroaxis is postulated as underlying the chronicity of pain. The transfer of pain to sites distant to that of the initial site of injury (for example, stroke resulting in chronic shoulder pain) may exist as a result of conveyance of cytokines, such as tumor necrosis factor-α (TNF α), IL-1β, and IL-6, along the neuroaxis or of enhanced cytokine signaling [1]. In addition, chronic pain can develop disproportionally to the initial injury. Therefore, the prescribed treatment is often ineffective in preventing the ensuing cycle of chronic pain that becomes even more difficult to treat medically. Patients with diverse chronic pain states have reduced brain region volumes, linking the brain to chronic pain. Prolonged, elevated TNF α may reduce gray matter volume, since increased TNF α appears to decrease neurogenesis in a neuropathic pain model and enhances production of glutamate, which is neurotoxic when in excess [2-4]. Interestingly, chronic low back pain patients treated with morphine show reduced gray matter volume [5]. Thus, ample evidence indicates TNF α as a key mediator of chronic pain, and its dysregulated production in the CNS is vital to pain chronicity.

A neuro-immunologic approach to comprehending the etiology and pathogenesis of chronic pain has gained popularity over recent years. This approach has evolved through awareness that a myriad of injury types in association with their concomitant inflammation will trigger bidirectional communications between the nervous system (neurons) and the immune system (inflammatory cells) [1,6]. The balanced release of pro- and anti-inflammatory cytokine proteins, as well as neurotransmitters such as norepinephrine, orchestrates the ensuing inflammatory response, which normally proceeds to injury resolution. If this active process fails (failure of resolution of injury), the pro-inflammatory state will persist, or an exaggerated post-traumatic inflammatory response will occur, leading to chronic inflammation. The resultant shift that favors a pro-inflammatory profile over an anti-inflammatory profile signifies loss of physiological homeostasis and is a harbinger of disease onset that includes the expression of chronic pain. This novel understanding of the role of neuroimmunology in the pathogenesis of brain disorders offers new approaches for pioneering breakthroughs.

Therefore, it is obvious that a comprehensive understanding of the etiologies, the pathophysiologic mechanisms, and the mediators contributing to the incidence of chronic pain are key to the development of an efficacious treatment for this devastating disorder. These mechanisms and mediators include pro-inflammatory cytokines, most significantly the pleiotropic neuromodulator and inflammatory mediator TNF α, various neurotransmitters, particularly norepinephrine, and neuroanatomical pathways and structures, including higher cortical brain regions. Our studies have focused on the role of the elevated levels of TNF α that is associated with chronic pain [7-9]. We hypothesize that TNF α over-expression in higher centers of the brain is crucial to expression of chronic pain, whether TNF α is increased locally in the brain during TBI or induced in the brain following an extremity affliction, and serves as a therapeutic target for the management of chronic pain.

Clinically, it is difficult to direct compounds such as anti-TNF α agents to the brain. Biologics (antibodies, antibody fragments, and fusion proteins) that target cytokines are large molecules that do not penetrate well into the CNS. Very little of these biologic agents get to the brain when delivered peripherally and therefore will have little effect on this organ. Direct intracerebroventricular injection is used in basic science research, but this invasive method is not practical for patients. Intrathecal injection is often employed in the clinical setting to deliver agents to the cerebrospinal fluid. However, this method of delivery is invasive and limited with only partial distribution to the ventricles, and with the remainder of the injection having alternate peripheral distribution. Thus, it is apparent that therapy for many neurological disorders requires a more direct route for drug delivery/access to the brain-the perispinal route offers this access [10].

We had been aware of reports in the scientific literature concerning treatment of neurodegenerative disorders with the TNF α inhibitor etanercept, but on January 21, 2014 we had the privilege of first-hand participation in the perispinal (injection in the peripheral vascular

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plexus, which lies outside of the spinal cord and thus not in the central nervous system) etanercept treatment of a patient suffering severe chronic neurological dysfunction over the span of three years due to a brain injury [11]. This patient had exhausted every treatment option available without adequate relief of pain, cognitive recovery, or regain of functional abilities. An alternative treatment option that attenuates levels of TNF α within the brain was sought; this treatment involves perispinal injection of etanercept, a human TNF α receptor-2 fusion protein that blocks activity of pro-inflammatory TNF α. The delivery consists of a non-invasive peripheral perispinal injection in the posterior neck region (into the posterior venous plexus), which allows for direct drug access to the brain ventricles via the choroid plexus following Trendelenburg positioning. Within minutes of receiving perispinal etanercept, the patient exhibited a profound response: her neuropathic pain was immediately relieved (i.e., within three minutes), slight facial droop disappeared, aphasia and speech impediments were resolved, and her motor coordination and cognitive ability returned (in comparison to pre-treatment evaluations, which both of the authors personally witnessed). We have followed-up to find that the patient's recovery persisted, and importantly, all with just a single injection of etanercept [11]. Our personal observations of perispinal etanercept injection with Trendelenburg positioning and the immediate neurological improvement produced were congruent with those reported for a series of over 600 consecutive patients [12]. While considerable improvement generally occurs after a single injection, some patients have chosen to receive a second and/or third treatment with perispinal etanercept. Remarkably, as per patient follow-up ranging from three weeks to three months, the duration of the response may be enduring unless the person experiences another insult to their brain [12,13]. This response is most exciting, especially considering that this method has been successfully utilized for patient care for more than a decade.

The published clinical results by Dr. Tobinick and colleagues support our many years of preclinical research, which show that blocking TNF α centrally (specifically in the brain) rapidly mitigates neuroinflammation, thereby affecting neuroplasticity and synaptic neurotransmission [7-9,14-17]. We theorize that the over expression of TNF α within the brain is responsible for neuropathic pain and neurologic dysfunction. The fact that off-label use (treatment of post-stroke/TBI neurological dysfunction) of FDA-approved etanercept via perispinal delivery is extremely rapid and therapeutically effective indicates the need for rigorous scientific investigation and clinical trials to further define the mechanisms mediating these rapid and profound neurological effects in order to procure FDA approval for the use of etanercept in treatment of people suffering from post-stroke and TBI disability. Importantly, this novel delivery of etanercept offers a safer, less intrusive treatment as described below. This perispinal method is used to administer etanercept for brain disorders; patients that receive perispinal etanercept for stroke/TBI report vast pain recovery [11,13,18]. We propose perispinal injection of anti-TNF α biologics as a chronic pain therapy that will rapidly (within minutes) increase brain neurotransmitter availability and avoid the significant adverse systemic effects of current treatments. As basic academic science researchers, we have published numerous discoveries regarding TNF α and how it regulates neuron function in the brain, which spans more than 26 years of investigations.

Our research has shown that either blocking pathologic TNF α activity or decreasing TNF α production that is produced solely in the brain (avoiding peripheral distribution) has profound patient benefits mediated through the reduction and/or amelioration of associated brain inflammation. Excess or prolonged inflammation can cause damage to tissues and in particular the brain parenchyma. Excess inflammation is usually abnormal, and the administration of specific anti-TNF α compounds can reduce or arrest this inflammatory response effectively, because TNF α is a proximal pro-inflammatory mediator. Certainly, achieving reduced inflammation in the brain at an appropriate time after succumbing to an insult such as TBI or stroke can restore appropriate brain functions. At such a time viable tissue remains in a dysfunctional state due to abnormal, unnecessary levels of TNF α. Therefore, it is expected that administration of etanercept *via* perispinal injection should achieve a very efficient decrease in TNF α expression throughout the brain parenchyma. Our preclinical research discoveries are paving the way for this treatment modality that blocks TNF α action in the brain [7,9].

As a key neuromodulator, the normal rapid production of TNF α is beneficial; but when this mediator is produced in excess for prolonged time periods, it contributes to neurotoxicity. In fact, TNF α was originally characterized in immunology as a double-edge sword. We have shown that exposure of neurons to TNF α within minutes affects neurotransmitter release in an *ex vivo* brain slice model system [8, 14-16]. We have also shown that exposure of brain tissue to TNF α within minutes changes second messenger G-protein coupling of neurotransmitter receptors [17]. Therefore, TNF α not only directs neurotransmitter release, but also directs the ability of neurotransmitters to elicit a response, both of which occur very rapidly. Removal of excess TNF α would consequently have profound effects on both of those responses. We have confirmed this by administering TNF α antibodies and nanoparticle complexed TNF α siRNA directly into the brain in animal models [7,9,19]. These findings, along with the scientific evidence considered in our 2014 reviews [20,21], demonstrate that rapid effects of blocking TNF α activity solely within the brain are entirely compatible with brain physiology.

Increasing basic science discoveries and clinical evidence suggest the potential to uniquely alleviate the enormous unmet medical need produced by chronic neuropathic pain from multiple causes, including stroke, TBI, diabetic neuropathy, and spinal cord injury. Unfortunately, the use of chronic opioids for pain has created a national emergency of opioid addiction and excess mortality. Using perispinal etanercept delivery to discogenic back pain patients, all reported substantial, sustained recovery verified by reduction in Oswestry score [13]. Also, patients *reduced significantly or completely discontinued* analgesic medication after perispinal etanercept. This included 11 of 20 patients requiring chronic opioids [13]. These case reports provide compelling evidence that targeting TNF *in the brain* is analgesic. Therefore, along with the potential for neurologic recovery, perispinal etanercept provides a viable alternative (non-opioid) treatment option for hard-to-treat chronic neuropathic pain.

The remarkable positive effect perispinal etanercept injection had on correcting the neurologic dysfunction of a patient who suffered a brain injury is evidence of translational medicine, that is, application of physiologic mechanisms discovered through basic science research to clinical practice [11, 20,21]. Consequently, in the absence of effective therapeutic intervention, perispinal etanercept injection for rapid and sustained treatment of post-stroke neurologic dysfunctions appears to provide significant improvements. In fact, the rapid response to modifying TNF α levels, and thus dampening TNF α signaling, may be involved in a myriad of brain pathologies (TBI, stroke-induced neurologic disabilities, Alzheimer's disease, and chronic pain), since many (if not all) are involved with altered neurotransmission. This direct, noninvasive treatment approach for gaining access to the ventricles and thus brain parenchyma is a pioneering discovery with ramifications for numerous brain disorders. It is anticipated that this treatment paradigm will quickly be moved to clinical trials and implemented globally. It is our hope that the medical and scientific communities will be inspired and driven by the quest for knowledge, understanding, and alleviation of needless suffering and thus embrace perispinal etanercept treatment not only for brain injury-induced pathologies and subsequent disabilities, but also for hard-to-treat chronic pain conditions.

References

1. Ignatowski TA, Samankan S, Spengler RN (2015) Chapter 3: Molecular Pathophysiology and the Role of TNF in the Neuro-inflammatory Reflex. In: CRPS: Past, Present & Future; Nader ND and Visnjevac O (eds). NOVA Science Publishers, Inc., Hauppauge, New York.
2. Clark IA, Vissel B (2016) Excess cerebral TNF causing glutamate excitotoxicity rationalizes treatment of neurodegenerative diseases and neurogenic pain by anti-TNF agents. J Neuroinflammation 13: 236-251.
3. Dellarole A, Morton P, Brambilla R, Walters W, Summers S, et al. (2014) Neuropathic pain-induced depressive-like behavior and hippocampal neurogenesis and plasticity are dependent on TNFR1 signaling. Brain Behav Immun 41: 65-81.
4. Pickering M, Cumiskey D, O'Connor JJ (2005) Actions of TNF-alpha on glutamatergic synaptic transmission in the central nervous system. Exp Physiol 90: 663-670.
5. Lin JC, Chu LF, Stringer EA, Baker KS, Sayyid ZN, et al. (2015) One month of oral morphine decreases gray matter volume in the right amygdala of individuals with low back pain: Confirmation of previously reported magnetic resonance imaging results. Pain Med 17: 1497-1504.
6. Fasick V, Spengler RN, Samankan S, Nader ND, Ignatowski TA (2015) The hippocampus and TNF: Common links between chronic pain and depression. Neurosci Bio behav Rev 53:139-159.
7. Ignatowski TA, Covey WC, Knight PR, Severin CM, Nickola TJ, et al. (1999) Brain-derived TNF α mediates neuropathic pain. Brain Res 841: 70-77.
8. Covey WC, Ignatowski TA, Knight PR, Spengler RN (2000) Brain-derived TNF α: Involvement in neuroplastic changes implicated in the conscious perception of persistent pain. Brain Res 859: 113-122.
9. Gerard E, Spengler RN, Bonoiu AC, Davidson BA, Mahajan SD, et al. (2015) Chronic constriction injury-induced nociception is relieved by nanomedicine-mediated decrease of rat hippocampal tumor necrosis factor. Pain 156: 1320-1333.
10. Tobinick EL (2016) Perispinal delivery of CNS drugs. CNS Drugs 30: 469-480.
11. Tobinick E, Rodriguez-Romanacce H, Levine A, Ignatowski TA, Spengler RN (2014) Immediate neurological recovery following perispinal etanercept years after brain injury. Clin Drug Invest 34: 361-366.
12. Tobinick E, Kim NM, Reyzin G, Rodriguez-Romanacce H, DePuy V (2012) Selective TNF inhibition for chronic stroke and traumatic brain injury: An observational study involving 629 consecutive patients treated with perispinal etanercept. CNS Drugs 26: 1051-1070.
13. Tobinick E, Davoodifar S (2004) Efficacy of etanercept delivered by perispinal administrationfor chronic back and/or neck disc-related pain: A study of clinical observations in 143patients. Curr Med Res Opin 20: 1075-1085.
14. Ignatowski TA, Spengler RN (1994) Tumor necrosis factor- α: Presynaptic sensitivity is modified after antidepressant drug administration. Brain Res 665: 293-299.
15. Ignatowski TA, Noble BK, Wright JR, Gorfien JL, Spengler RN (1996) TNF α: A neuromodulator in the central nervous system. Adv Exp Med Biol 402: 219-224.
16. Ignatowski TA, Noble B, Wright JR, Gorfien J, Heffner RR, et al. (1997) Neuronal-associated tumor necrosis factor (TNF α): Its role in noradrenergic functioning and modification of its expression following antidepressant administration. J Neuroimmunol 79: 84-90.
17. Reynolds JL, Ignatowski TA, Spengler RN (2005) Effect of TNF α on the reciprocal G-protein induced regulation of norepinephrine release by the α2-adrenergic receptor. J Neurosci Res 79: 779-787.
18. Tobinick E (2009) Perispinal etanercept for neuroinflammatory disorders. Drug Discov Today 14: 168-177.
19. Reynolds JL, Ignatowski TA, Sud R, Spengler RN (2004) Brain-derived tumor necrosis factor-α and its involvement in noradrenergic neuron functioning involved in the mechanism of action of an antidepressant. J Pharmacol Exp Ther 310: 1216-1225.
20. Ignatowski TA, Spengler RN, Dhandapani KM, Folkersma H, Butterworth RF, et al. (2014) Perispinal Etanercept for Post-stroke Neurological and Cognitive Dysfunction: Scientific Rationaleand Current Evidence. CNS Drugs 28: 679-697.
21. Ignatowski TA, Spengler RN, Tobinick E (2014) Authors' Reply to Whitlock: Perispinal Etanercept for Post-stroke Neurological and Cognitive Dysfunction: Scientific Rationale and Current Evidence. CNS Drugs 28: 1207-1213.