

Neurotrophic factors and tension-type headache: another brick in the wall?

Fatores neurotróficos na cefaleia do tipo tensional: mais um tijolo na parede?

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Tension-type headache (TTH) is the most prevalent primary headache and the second most prevalent disorder in the world¹. However, despite the great progress made in understanding the putative physiological and biological abnormalities of migraines in recent decades², the same cannot be said for their counterpart, TTH, which has been relegated to the background by most investigators³ and, now neglected⁴, can be considered the “ugly duckling” of headache disorders classified by the International Headache Society (IHS). In what is perhaps a vicious circle, few initiatives have been taken by independent academic or industry-financed researchers to change this situation.

The physiological basis of TTH was explored in the 1990s⁵, and the findings allowed hypotheses for putative biochemical mechanisms associated with this type of headache to be drawn up⁶. Nevertheless, these hypothetical mechanisms have yet to be confirmed and, with few exceptions, the studies that have been carried out did not use animal models or test these mechanisms to the same level of detail as in migraine studies².

It is against this background that the paper in this edition by Domingues et al., who studied the role of neurotrophic factors in TTH down to the molecular level, acquires particular importance⁷. In a well-designed and carefully conducted cross-sectional study, Domingues et al. determined serum levels of brain-derived neurotrophic factor (BDNF), nerve-growth factor (NGF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5) in forty-eight TTH patients and forty-eight age and gender-matched controls. The authors searched for a correlation between these neurotrophic factors and TTH (both episodic and chronic) as well as other measurable psychosocial variables⁷.

Early studies of the pathophysiology of TTH supported the muscle-contraction theory, although TTH can occur with or without pericranial tenderness. The widespread acceptance this theory gained can be observed in a review by Maekawa et al.⁸, who discussed the factors supporting and refuting the putative role of adrenergic receptors and muscle hypoperfusion in myofascial pain.

Following a different line of investigation, and probably considering the similarities between migraine and TTH, such as their sharing of common triggers^{3,9}, Ashina et al. searched unsuccessfully for changes in neuropeptides such as substance P, neuropeptide Y and vasoactive intestinal polypeptide (VIP) in peripheral blood of patients with chronic tension-type headache (CTTH)^{10,11}. Their findings may have in fact been anticipated by Bach et al., who found normal levels of calcitonin gene-related peptide (CGRP) in the cerebrospinal fluid of patients with TTH^{12,13}. To date, the most consistent finding in the pathophysiology of CTTH has been the evidence that glyceryl-nitrate (GNT) infusion can induce late-onset tension-type-like headache in CTTH sufferers^{14,15}. These findings prompted a cross-over trial, which showed that NG-monomethyl-L-arginine hydrochloride (L-NMMA), an NOS inhibitor, decreases CTTH pain¹⁶. The authors hypothesized that NG-monomethyl-L-arginine hydrochloride (L-NMMA) may act on sensitized neurons. Neural sensitization in CTTH is far more than a hypothesis: there is plenty of indirect evidence for sensitization in CTTH, such as a slower recovery cycle of the R2 blink reflex in TTH¹⁷. On the other hand, the finding of a paradoxical facilitation of the R3 reflex response during the cold pressor test¹⁷ pointed to an associated deficient descending inhibition¹⁸. To further complicate the puzzle, individuals with TTH were found to have increased pericranial muscle tenderness even in the absence of headache¹⁷. However, a study with 100 individuals found that CTTH subjects had normal pain thresholds prior to the

development of CTTH but that these thresholds decreased in individuals who developed CTTH, suggesting that pain hypersensitivity is a consequence of frequent TTHs¹⁹. This sensitization is thought to be responsible for the pericranial tenderness²⁰ and hyperalgesia of neck and shoulder muscles in CTTH patients²¹. Nonetheless, the mechanism of central sensitization²² is not completely understood and may depend on “hyperalgesic priming”, a process that in turn depends on the epsilon isoform of protein kinase C (PKCε) and a switch in intracellular signaling pathways that mediate cytokine-induced nociceptor hyperexcitability²³.

In this scenario the relevance of neurotrophic factors, which are considered by some researchers to be essential for neuronal plasticity, becomes more evident, justifying the efforts of Domingues et al.⁷.

NEUROTROPHIC FACTORS

The existence of neurotrophic factors was first posited in 1939 by Hamburger and resulted in the proposal by Levi-Montalcini and Levi that they are essential to ensure the survival of differentiating neurons. In 1949 this hypothesis was supported by the work of Hamburger and Levi-Montalcini²⁴. The experimental work of Levi-Montalcini in the 1940s and the purification of NGF in the 1960s by Stanley Cohen led both to win the 1986 Nobel Prize for Physiology or Medicine. The mature forms of all neurotrophins interact with their respective high-affinity tropomyosin kinase receptors (TrkA and TrkB/NGF; BDNF/NT-4; and TrkC/NT-3) but also bind to the p75 neurotrophin receptor with low affinity²⁵.

While Trk receptors are associated with cell survival, neurite growth, cell differentiation and neural plasticity, p75 receptors are associated with cell-cycle arrest, cell death and inhibition of neurite growth (Figure)²⁶. It has been suggested that activated Trk receptors can have local and/or retrograde action through different pathways²⁵.

The neurophysiology of nociception is based on the detection of noxious stimuli by nociceptors present in practically all organs. Nociceptors are small-diameter sensory neuron terminals (A fibers), most of which are polymodal and respond to noxious mechanical (pressure), thermal (heat and cold) and chemical stimuli²⁷. Depolarization of these receptors causes voltage-gated sodium channels to open and, consequently, results in the generation of action potentials that propagate to the dorsal horn of the spinal cord. The release by nerve endings of substance P and a peptide genetically related to calcitonin in neurovascular junctions leads to vasodilation and plasma extravasation, causing neurogenic inflammation and nociceptor sensitization. The nociceptive threshold falls and fiber nociceptors respond more intensely to noxious stimuli than when they are not sensitized. Furthermore, the inflammatory process activates silent C fiber nociceptors and favors nociception secondary to mechanical or thermal stimuli

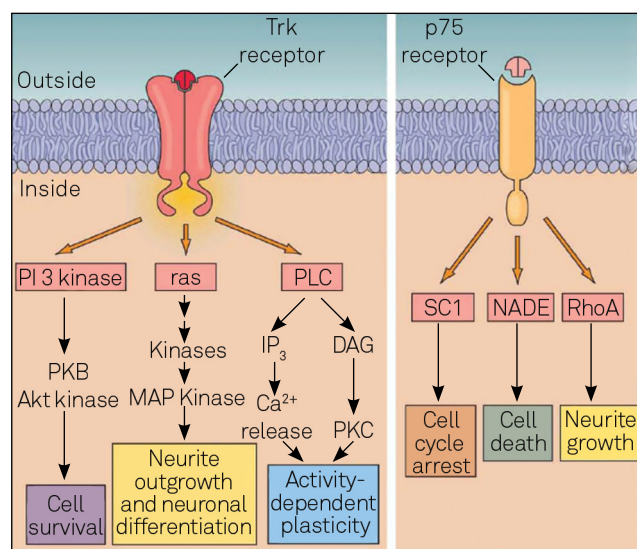
(central sensitization), with abnormal characteristics of nociceptive pain, i.e., allodynia and hyperalgesia^{28,29}. This nociceptive activation promotes rapid structural changes and a long-lasting increase in synaptic strength, resulting in hyperalgesia²⁹.

Studies have shown elevated intraneuronal NGF levels during inflammatory processes. These increased levels are associated with increased BDNF expression, which, although not contributing to the processing of nociceptive information in normal circumstances, contributes to inflammatory hypersensitivity³⁰. It has been reported that the use of a receptor-inactivating protein (TrkA-IgG) to block the effects of endogenous NGF resulted in a reduction in sensitivity to thermal stimuli but no change in sensitivity to mechanical stimuli, showing that peripheral sensitivity can be regulated by NGFs³¹. Bennett (2001) notes that increased levels of NGF produce both short-term thermal hyperalgesia and mechanical and thermal hyperalgesia over time²⁹. Studies in knock-out rats suggest that NGF and TrkA are the mediators most closely associated with nociceptive pathways³³ (Table).

In addition, NGFs are not only important in the acute phase of the pain process but can also exert long-term effects on nociception by regulating B1 and B2 bradykinin, VR1 vanilloid and sodium channel receptors among others³⁴.

In short, neurotrophic factors are important modulators of the processing of nociceptive information in the peripheral and central nervous systems as they act on the pathophysiology of pain; NGF and BDNF antagonists are therefore potential therapeutic alternatives for pain management.

Readers can find further information about the findings of Domingues et al.⁷ on the role of NF in TTH in their paper published in this issue. Whether their results confirm or reject their hypothesis, they remain consistent and will undoubtedly strengthen the wall of knowledge on TTH.



Modified from: Huang SH. Neurotrophic factors and their receptors²⁶.

Figure. Neurotrophic factors receptors and the effects of their activation.

Table. Sensory modalities losses and percentages of dorsal root ganglia neuronal loss in neurotrophic factors/receptors knocked-out mice.

Neurotrophics factors		
Mutation	Neuronal loss %	Sensory modality
NGF	80	Nociceptors, thermoreceptors, low-threshold, mechanoreceptors
BDNF	30	Mechanoreceptors (Meissner)
NT-3	60	Proprioceptors, D-hair receptors, and mechanoreceptors
NT-4/5	0	-
Neurotrophic factors receptors		
Mutation	Neuronal loss %	Sensory modality
trkA	80	Nociceptors, thermoreceptors, low-threshold, mechanoceptors
trkB	30	Mechanoceptors (Meissner)
trkC	20-30	Proprioceptors

NGF: nerve-growth factor; BDNF: brain-derived neurotrophic factor; NT-3: neurotrophin-3, NT-4/5: neurotrophin-4/5. Modified from Fariñas et al.³³.

References

- Martelletti P, Birbeck GL, Katsarava Z, Jensen RH, Stovner LJ, Steiner TJ. The Global Burden of Disease survey 2010. Lifting The Burden and thinking outside-the-box on headache disorders. *J Headache Pain* 2013;14(1):13. <http://dx.doi.org/10.1186/1129-2377-14-13>
- Pietrobon D, Moskowitz MA. Pathophysiology of migraine. *Annu Rev Physiol*. 2013;75(1):365-91. <http://dx.doi.org/10.1146/annurev-physiol-030212-183717>
- Yu S, Han X. Update of chronic tension-type headache. *Curr Pain Headache Rep*. 2015;19(1):469. <http://dx.doi.org/10.1007/s11916-014-0469-5>
- Bendtsen L, Jensen R. Tension-type headache: the most common, but also the most neglected, headache disorder. *Curr Opin Neurol*. 2006;19(3):305-9. <http://dx.doi.org/10.1097/01.wco.0000227043.00824.a9>
- Jensen R. Peripheral and central mechanisms in tension-type headache: an update. *Cephalalgia* 2003;23(1 Suppl 1):49-52. <http://dx.doi.org/10.1046/j.1468-2982.2003.00574.x>
- Ashina S, Bendtsen L, Ashina M. Pathophysiology of tension-type headache. *Curr Pain Headache Rep*. 2005;9(6):415-22. <http://dx.doi.org/10.1007/s11916-005-0021-8>
- Domingues RB, Duarte H, Rocha NP, Teixeira AL. Neurotrophic factors in tension-type headache. *Arq Neuropsiquiatr* 2015;73(5):420-24. <http://dx.doi.org/10.1590/0004-282X20150036>
- Maekawa K, Clark GT, Kuboki T. Intramuscular hypoperfusion, adrenergic receptors, and chronic muscle pain. *J Pain*. 2002;3(4):251-60. <http://dx.doi.org/10.1054/jpai.2002.125923>
- Ailani J. Tension-type headache and women: do sex hormones influence tension-type headache? *Curr Pain Headache Rep*. 2010;14(6):436-40. <http://dx.doi.org/10.1007/s11916-010-0144-4>
- Ashina M, Bendtsen L, Jensen R, Ekman R, Olesen J. Plasma levels of substance P, neuropeptide Y and vasoactive intestinal polypeptide in patients with chronic tension-type headache. *Pain*. 1999;83(3):541-7. [http://dx.doi.org/10.1016/S0304-3959\(99\)00159-1](http://dx.doi.org/10.1016/S0304-3959(99)00159-1)
- Ashina M, Bendtsen L, Jensen R, Schifter S, Jansen-Olesen I, Olesen J. Plasma levels of calcitonin gene-related peptide in chronic tension-type headache. *Neurology* 2000;55(9):1335-40. <http://dx.doi.org/10.1212/WNL.55.9.1335>
- Bach FW, Langemark M, Ekman R, Rehfeld JF, Schifter S, Olesen J. Effect of sulpiride or paroxetine on cerebrospinal fluid neuropeptide concentrations in patients with chronic tension-type headache. *Neuropeptides*. 1994;27(2):129-36. [http://dx.doi.org/10.1016/0143-4179\(94\)90053-1](http://dx.doi.org/10.1016/0143-4179(94)90053-1)
- Edvinsson L, Uddman R. Neurobiology in primary headaches. *Brain Res Brain Res Rev*. 2005;48(3):438-56. <http://dx.doi.org/10.1016/j.brainresrev.2004.09.007>
- Ashina M, Bendtsen L, Jensen R, Olesen J. Nitric oxide-induced headache in patients with chronic tension-type headache. *Brain* 2000;123(9):1830-7. <http://dx.doi.org/10.1093/brain/123.9.1830>
- Olesen J. The role of nitric oxide (NO) in migraine, tension-type headache and cluster headache. *Pharmacol Ther*. 2008;120(2):157-71. <http://dx.doi.org/10.1016/j.pharmthera.2008.08.003>
- Ashina M, Lassen LH, Bendtsen L, Jensen R, Olesen J. Effect of inhibition of nitric oxide synthase on chronic tension-type headache: a randomised crossover trial. *Lancet*. 1999;353(9149):287-9. [http://dx.doi.org/10.1016/S0140-6736\(98\)01079-4](http://dx.doi.org/10.1016/S0140-6736(98)01079-4)
- Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*. 2011;152(3 Suppl):S2-15. <http://dx.doi.org/10.1016/j.pain.2010.09.030>
- Sandrini G, Rossi P, Milanov I, Serrao M, Cecchini AP, Nappi G. Abnormal modulatory influence of diffuse noxious inhibitory controls in migraine and chronic tension-type headache patients. *Cephalalgia*. 2006;26(7):782-89. <http://dx.doi.org/10.1111/j.1468-2982.2006.01130.x>
- Coppola G, Di Lorenzo C, Schoenen J, Pierelli F. Habituation and sensitization in primary headaches. *J Headache Pain*. 2013;14(1):65. <http://dx.doi.org/10.1186/1129-2377-14-65>
- Tommaso M, Libro G, Guido M, Sciriuocchio V, Losito L, Puca F. Heat pain thresholds and cerebral event-related potentials following painful CO2 laser stimulation in chronic tension-type headache. *Pain* 2003;104(1-2):111-9. [http://dx.doi.org/10.1016/S0304-3959\(02\)00485-2](http://dx.doi.org/10.1016/S0304-3959(02)00485-2)
- Fernández-de-las-Peñas C, Ge HY, Cuadrado ML, Madeleine P, Pareja JA, Arendt-Nielsen L. Bilateral pressure pain sensitivity mapping of the temporalis muscle in chronic tension-type headache. *Headache* 2008;48(7):1067-75. <http://dx.doi.org/10.1111/j.1526-4610.2007.01005.x>
- Fernández-de-Las-Peñas C, Madeleine P, Caminero AB, Cuadrado ML, Arendt-Nielsen L, Pareja JA. Generalized neck-shoulder hyperalgesia in chronic tension-type headache and unilateral migraine assessed by pressure pain sensitivity topographical maps of the trapezius muscle. *Cephalalgia* 2010;30(1):77-86. <http://dx.doi.org/10.1111/j.1468-2982.2009.01901.x>
- Reichling DB, Levine JD. Critical role of nociceptor plasticity in chronic pain. *Trends Neurosci*. 2009;32(12):611-8. <http://dx.doi.org/10.1016/j.tins.2009.07.007>
- Hamburger V, Levi-Montalcini R. Proliferation, differentiation and degeneration in the spinal ganglia of the chick embryo under normal and experimental conditions. *J Exp Zool*. 1949;111(3):457-501.

25. Skeldal S, Matusica D, Nykjaer A, Coulson EJ. Proteolytic processing of the p75 neurotrophin receptor: a prerequisite for signalling? Neuronal life, growth and death signalling are crucially regulated by intra-membrane proteolysis and trafficking of p75(NTR). *BioEssays*. 2011;33(8):614-25. <http://dx.doi.org/10.1002/bies.201100036>
26. Huang S-H. Neurotrophic factors and their receptors [35 slides]. [date unknown] [cited 2015/03/14]. Available from: <http://www.neurobio.sdu.edu.cn/download/ppt/Neurotrophic%20factors%20and%20Their%20receptors.pdf>
27. Schaible HG, Del Rosso A, Matucci-Cerinic M: Neurogenic aspects of inflammation. *Rheum Dis Clin North Am* 2005;31(1):77-101. <http://dx.doi.org/10.1016/j.rdc.2004.09.004>
28. Gold MS, Gebhart GF. Nociceptor sensitization in pain pathogenesis. *Nat Med*. 2010;16(11):1248-57. <http://dx.doi.org/10.1038/nm.2235>
29. Bennett DL. Neurotrophic factors: important regulators of nociceptive function. *Neuroscientist*. 2001;7(1):13-7. <http://dx.doi.org/10.1177/107385840100700105>
30. Schaible HG, Ebersberger A, Natura G. Update on peripheral mechanisms of pain: beyond prostaglandins and cytokines. *Arthritis Res Ther*. 2011;13(2):210. <http://dx.doi.org/10.1186/ar3305>
31. Lewin GR, Nykjaer A. Pro-neurotrophins, sortilin, and nociception. *Eur J Neurosci*. 2014;39(3):363-74. <http://dx.doi.org/10.1111/ejn.12466>
32. McMahon SB, Bennett DL, Priestley JV, Shelton DL. The biological effects of endogenous nerve growth factor on adult sensory neurons revealed by a trkA-IgG fusion molecule. *Nat Med*. 1995;1(8):774-80. <http://dx.doi.org/10.1038/nm0895-774>
33. Fariñas I, Cano-Jaimez M, Bellmunt E, Soriano M. Regulation of neurogenesis by neurotrophins in developing spinal sensory ganglia. *Brain Res Bull*. 2002;57(6):809-16. [http://dx.doi.org/10.1016/S0361-9230\(01\)00767-5](http://dx.doi.org/10.1016/S0361-9230(01)00767-5)
34. Fjell J, Cummins TR, Fried K, Black JA, Waxman SG. In vivo NGF deprivation reduces SNS expression and TTX-R sodium currents in IB4-negative DRG neurons. *J Neurophysiol*. 1999;81(2):803-10.