NEUROANATOMY

TRPA1: A Ghost ship in the membrane

Transient Receptor Potential Ankyrin 1 is a calcium-permeable channel that plays a major role in pain perception, overactivity of these cation channels can induce hyperalgesia. A number of compounds belonging to various chemical families that were involved in animal/human studies have been demonstrated to act as antagonists to this TRP class of channel proteins and attenuate symptoms of hyperalgesia.

Micah Black

The old adage “nociception is pain perception, anti-nociception is the prevention of pain perception” has been a primary focus for researchers in the medical fields as well as the peripheral fields of chemical research. Nociceptive nervous tissue expresses myriad membrane-bound proteins, foremost of which are a specialized class of channel proteins referred to as transient receptor potential (TRP) proteins. They are expressed on primary afferent neurons[1], astrocytes[2], oligodendrocytes[3] and Schwann cells[4]. When activated, TRP proteins electrically communicate information to the nociceptor regarding noxious or potentially harmful stimuli and can initiate flexion reflexes in the organism. Hyperalgesia (hypersensitivity to pain) has been attributed to a variety of genetic and environmental factors. Clinically, sleep deprivation has been attributed to hyperalgesia[5] by generating chemicals that amplify pain signals through TRP pathways[6,7]. Chemical imbalances due to other factors such as chemotherapy can also induce symptoms of hyperalgesia, initiating a cascade of activity on TRP pathways and effectively causing the organism to experience heightened levels of pain that is debilitating.

A study published by the Journal of Pharmaceuticals describes research involving derivatives of xanthine, oxime, and benzamide[8] that have been demonstrated to prevent the TRP from activating (TRP antagonist). The oxime derivatives were not effective when taken orally by humans, but were clinically effective in rat models[8]. Conversely, a number of trichloro(sulfanyl)ethyl benzamide derivatives were demonstrated to exclusively effect human models as opposed to rat models[9]. TRP Ankyrin 1 (TRPA1) is implicated to participate in the model TRP nociception pathways. It is expressed in the above-listed cells and chemical mechanisms necessary for nociceptive signaling have been associated with TRPA1. In the case of sleep deprivation, NMDA-nitric oxide cascades as well as D-amino acid oxidase (DAAO) promote the activation of astrocytes in the dorsal horn of the spinal cord due to lack of sleep by generating metabolites that amplify nociceptive signals through TRPA1[10] as illustrated in figures 1.1 and 1.2.

In clinical studies, animal test subjects were injected with the TRPA1 antagonists in the spinal cord around the dorsal horn. Spinal administration of these compounds resulted in attenuated hyperalgesia, supporting the hypothesis that TRPA1 is expressed in the spinal cord as well as the protein’s participation in the transduction of pain signals[11]. Animal tests are useful for modeling conditions that result in pain hypersensitivity due to a variety of factors; ability to control their sleep patterns, availability of chemotherapy drugs implemented with symptoms of neuropathy/allodynia, and genetic modifications that make it possible to alter desired protein expression. Modulation of

TRPA1 expression in the nervous system of rat models has confirmed its presence in the viscera. Studying the TRP class of membrane-bound proteins provides a more complete picture of somatosensory and nociceptive pathways that are mediated by ligand-binding and metabolism of endogenous molecules induced by environmental stimuli as well as genetic factors.

Medical researchers strive to mitigate the side effects of treatment for various health problems. Diabetic nerve pain, chemotherapy induced neuropathy/allodynia, sleep induced hyperalgesia, post-operative pain and noxious stimuli are examples of factors that interact with the transient receptor potential proteins and produce symptoms of acute or chronic pain. Lack of sensitivity to agonist molecules can cause the TRP proteins to not function properly, creating an alternative issue of the absence of nociceptive stimulation. Reviewing the existing literature regarding these topics will provide yet another component to a more complete understanding of the mammalian nervous system, effectively resolving a portion of the innate difficulties with regard to medical care and treatment.

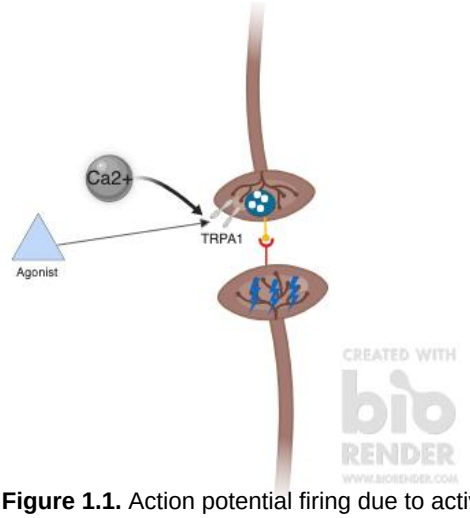

Figure 1.1. Action potential firing due to activation of TRPA1

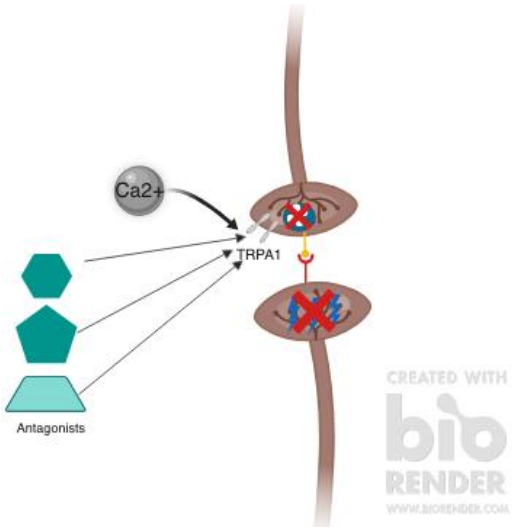

Figure 1.2. Action potential inhibited due to inhibition of TRPA1

REFERENCES

1. Story, G.M.; Peier, A.M.; Reeve, A.J.; Eid, S.R.; Mosbacher, J.; Hricik, T.R.; Earley, T.J.; Hergarden, A.C.; Andersson, D.A.; Hwang, S.W.; et al. ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. *Cell* 2003, *112*, 819–829.
2. Shigetomi, E.; Tong, X.; Kwan, K.Y.; Corey, D.P.; Khakh, B.S. TRPA1 channels regulate astrocyte resting calcium and inhibitory synapse efficacy through GAT-3. *Nat. Neurosci.* 2011, *15*, 70–80.
3. Hamilton, N.B.; Kolodziejczyk, K.; Kougioumtzidou, E.; Attwell, D. Proton-gated Ca^{2+}-permeable TRP channels damage myelin in conditions mimicking ischaemia. *Nature* 2016, *529*, 523–527.
4. De Logu, F.; Nassini, R.; Materazzi, S.; Carvalho Gonçalves, M.; Nosi, D.; Rossi Degl'Innocenti, D.; Marone, I.M.; Ferreira, J.; Li Puma, S.; Benemei, S.; et al. Schwann cell TRPA1 mediates neuroinflammation that sustains macrophage-dependent neuropathic pain in mice. Nat. Commun. 2017, 8, 1887.
5. Lautenbacher, S.; Kundermann, B.; Krieg, J.C. Sleep deprivation and pain perception. Sleep Med. Rev. 2006, 10, 357–369.
6. Wei, H.; Koivisto, A.; Saarnilehto, M.; Chapman, H.; Kuokkanen, K.; Hao, B.; Huang, J.L.; Wang, Y.X.; Pertovaara, A. Spinal transient receptor potential ankyrin 1 channel contributes to central pain hypersensitivity in various pathophysiological conditions in the rat. Pain 2011, 152, 582–591.
7. Wiertelak, E.P.; Furness, L.E.; Horan, R.; Martinez, J.; Maier, S.F.; Watkins, L.R. Subcutaneous formalin produces centrifugal hyperalgesia at a non-injected site via the NMDA-nitric oxide cascade. Brain Res. 1994, 649, 19–26.

8. McNamara, C.R.;MandelBrehm,J.;Bautista,D.M.;Siemens,J.;Deranian,K.L.;Zhao,M.;Hayward,N.J.; Chong, J.A.; Julius, D.; Moran, M.M.; et al. TRPA1 mediates formalin-induced pain. *Proc. Natl. Acad. Sci. USA* 2007, *104*, 13525–13530.
9. Klionsky, L.; Tamir, R.; Gao, B.; Wang, W.; Immke, D.C.; Nishimura, N.; Gavva, N.R. Species-specific pharmacology of Trichloro(sulfanyl)ethyl benzamides as transient receptor potential ankyrin 1 (TRPA1) antagonists. Mol. Pain 2007, 3, 39.
10. Zhang, G.H.; Lv, M.M.; Wang, S.; Chen, L.; Qian, N.S.; Tang, Y.; Zhang, X.D.; Ren, P.C.; Gao, C.J.; Sun, X.D.; et al. Spinal astrocytic activation is involved in a virally-Induced rat model of neuropathic pain. *PLoS ONE* 2011, *6*, e23059.
11. Chen, J.; Joshi, S.K.; DiDomenico, S.; Perner, R.J.; Mikusa, J.P.; Gauvin, D.M.; Segreti, J.A.; Han, P.; Zhang, X.F.; Noforatos, W. et al. Selective Blockade of TRPA1 Channel Attenuates Pathophysiological Pain Without Altering Noxious Cold Sensation or Body Temperature Regulation. *Pain* 2011, 152, 1165-1172.