DFL23693, a new TRPM8 antagonist, in wet-dog shake (WDS) by icilin and in a model of neuropathic pain

C. De Caro[1], R. Russo[1], C. Avagliano [1], C. Cristiano[1], G. La Rana[1], E. Aiello[1], L. Brandolini[2], G. Bianchini[2], A. Aramini[2], A. Calignano[1]

[1]Dept. of Pharmacy, University of Naples Federico II, Via D. Montesano 49, 80131 Naples, Italy
[2]Dompé farmaceutici S.p.A., Via Campo di Pile s.n.c., 67100 L'Aquila, Italy

Chronic neuropathic pain is an intractable pain with few effective treatments. It is often characterized by stimulus-independent persistent pain or abnormal sensory perception of pain, such as allodynia (pain perception upon the innocuous tactile stimuli) and hyperalgesia (exaggerated pain sensations by mildly noxious stimuli) (1,2). Recently, Transient Receptor Potential (TRP) channel family has been proposed to play an important role in thermosensation in mammals (3). Six thermosensitive ion channels of this family have been discovered, including TRPV1, TRPV2, TRPV3, TRPV4, TRPM8 and TRPA1. TRPM8 and TRPA1 are responsive to cold stimuli. TRP melastatin 8 (TRPM8) is expressed by a subpopulation of sensory neurons in dorsal root ganglia (DRG) and trigeminal ganglia (4, 5), where responses to cooling correlate well with mRNA expression and menthol sensitivity (6–8). In vitro, TRPM8 is activated by moderate cold (with a 22–27°C threshold) and exogenous 'cooling-mimetic' compounds, such as menthol and icilin (4). Several in vivo studies have shown that levels of TRPM8 protein (9) and mRNA (10) were both increased in rats with chronic neuropathic pain. This suggests that TRPM8 ion channel may be closely related to allodynia induced by neurological diseases.
Aim of this study was to evaluate effect of novel TRPM8 antagonist (Dompé's compound 'DFL23693') in icilin-induced WDS and in neuropathic pain by chronic constriction injury (CCI) following oral treatment.
Results showed that the lowest dose (3 mg/kg) did not produce analgesic activity, whereas the doses 10 and 30 mg/kg per os were effective, leading to a significant reduction of mechanical and cold allodynia at 7 and 14 days after ligation. In particular, the results indicate that the dose of 10 mg/kg showed its maximum activity 3 h after administration and tended to decrease 5 h after oral administration. The highest dose of DFL23693 (30mg/kg) produced a significant analgesic activity already 1h following oral administration, and this activity was kept until 5 h post dose. Moreover, in another set of experiments, DFL23693 was tested to assess the ability to block the spontaneous wet-dog shake, phenomenon induced by icilin. Icilin, a TRPM8 agonist, was administrated intraperitoneally (i.p.) at dose of 1mg/kg to induce an intermittent but rhythmic 'wet dog-like' shakes (WDS) of neck, head and trunk in each animal. Results showed that single oral administration of DFL23693 (10mg/kg) reduced significantly WDS, suggesting a reduction of TRPM8 activation.
In this study we have shown that Dompé's drug DFL23693 is a strong TRPM8 antagonist, as demonstrated in iclin-induced WDS. Moreover, CCI results indicate that oral DFL23693 treatment reduced hyperalgesia and allodynia in a dose- and time-dependent manner.

1. Ueda H., Pharmacol Ther (2006)
2. Bridges D., Br J Anaesth (2001)
3. Dhaka A., Annu Rev Neurosci (2006)
4. McKemy, D.D., Nature (2002)
5. Peier, A.M., Cell (2002)
6. Nealen, M.L., J. Neurophysiol., (2003)
7. Thut, P.D., Neuroscience. (2003)
8. Babes, A., Eur. J. Neurosci. (2004)
9. Xing H., J Neurosci (2007)
10. Frederick J., Biochem Biophys Res Commun (2007)