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Specific ion channels and intracellular signalling in a *C. elegans* thermonociceptor

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Pain is an unpleasant feeling with a protective function. In fact, it warns animals of possible threats that can lead to tissue damage. The physical feeling of pain is mediated by the nociception process. It involves the activation of specific sensory neurons innervating the body periphery and delivering the information to regions placed into the spinal cord and in the brain. Under pathological conditions, pain can be sensed in the absence of harmful stimuli and become chronic. The molecular mechanisms underlying acute and chronic pain are not completely clear and they require detailed investigation. The study of pain is difficult to perform in mammals, not only because of the technical challenges but also because of the ethical issues that concerns the experimental procedures. The nematode *C. elegans* is promising model to study nociception, whose nervous system has been mapped and the function of many sensory neurons has been characterised.

In this work, we characterised and identified key features that make the thermonociceptor FLP ia fruitful model for nociception studies. We show, by calcium imaging experiments *in vivo,* that FLP encodes thermal information in a tonic and graded manner over a wide range of thermal stimuli spanning from noxious cold to noxious heat (8-36°C). This tonic-signalling mode allows FLP to trigger sustained behavioural changes necessary for escape behaviour. In addition, we identified relevant ion channels that mediate different functions of FLP in response to thermal stimuli, such as Transient Receptor Potential, Voltage-gated Calcium, and sodium ‘leak’ channels. Surprisingly, the Ryanodine receptor resulted to be necessary to the neuronal long-lasting activation. Moreover, this receptor has the crucial role of adjusting the calcium levels in the FLP cytoplasm according to environmental temperature and modulating aversive behaviors.

We also focused our attention on the intracellular signalling activated by calcium in the FLP neuron, especially involving the Calcium-Calmodulin-dependent protein kinase (CaMK) pathway. By developing a new *C. elegans*-adapted FRET biosensor, we demonstrate that noxious heat provokes the phosphorylation of an important transcription factor, the CRE-response element-binding protein (CREB, CRH-1 in *C. elegans*) *in vivo*. The activation of CREB depends on the phosphorylation of a specific amino acidic residue and it results to be mediated by the *C. elegans* CaMK, CMK-1, and surprisingly, by PKA, another essential kinase. The role of CaMK and PKA on CREB phosphorylation might mediate short-term and long-term responses. This regulation is not clear yet and it and it requires further investigation.

All the results we present in this “Thesis” will hopefully inspire future studies about nociception and they could be translated to mammals in order to develop effective therapeutic strategies towards pain-related diseases.

Jury:

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