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Sensory adaptation driven by controlled CaM kinase-1 subcellular localization: dissection of the mechanisms in *C. elegans* thermosensory neurons

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To increase their chances of surviving in the natural environment, animals requires efficient defensive behaviours. Several abilities, including the capacity to sense noxious stimuli, nociception, and to elaborate the information to form learning and memories, are at the base of defensive behaviours. Indeed, previous sensory experiences can orient the nervous system to the achievement of optimized avoidance behaviours. Sensory-behaviour adaptation is considered one of the simplest forms of learning and is depending on a variety of neuronal plasticity mechanisms, still not fully understood.

C. elegans long-term adaptation to temperatures (noxious and innocuous) constitutes a interesting paradigm to study plasticity mechanisms. A previous study from the Glauser's lab indicated that in the pair of FLP polymodal nociceptors, Ca^{2+}/Calmodulin-dependent protein kinase-1 (CMK-1) translocates from the cytoplasm to the nucleus in response to prolonged heat stimulations (over 60' at 28°C), and that this translocation is necessary and sufficient to trigger the mechanisms leading to long-term desensitization to noxious heat. During my thesis, I dissected the molecular mechanisms controlling CMK-1 subcellular localization and shed light on the pathway linking long-term cell activity to CMK-1 subcellular re-distribution, which is involved in long-term behavioral adaptation and gene expression regulation, in the two main thermosensory neurons (FLP and AFD).

My thesis shows that (i) a pair of classical localization signals (NES/NLS) make CMK-1 able to perform nucleocytoplasmic shuttling in and out the nucleus, via the canonical importin/exportin pathways, (ii) the binding of CMK-1 to Ca^{2+}/CaM complex is accountable to promote its nuclear import. Finally, I provide additional proofs that the active regulation of CMK-1 subcellular distribution in sensory neurons is an important requirement to maintain a physiological sensory plasticity, in both *C. elegans* thermosensory neurons (FLP and AFD), and a proper experience-dependent behavioural plasticity.

Through the dissection of the elements defining CMK-1 subcellular localization, my work provides a better understanding of the molecular bases of intrinsic thermonociceptor's plasticity.

CMK-1 is emerging as major regulator of *C. elegans* behaviours, so I propose that similar mechanisms are likely to exist for other sensory modalities. Furthermore, given the high similarity between *C. elegans* and mammalian CaM kinases, analogous molecular mechanisms might regulate pain sensitivity in humans. Malfunctional nociceptive plasticity is related to the onset of debilitating pathological phenomena, like chronic pain and hyperalgesia. Thus, the results described in my thesis might constitute a good starting point to acquire information useful to develop better strategies to treat pathological pain.

Jury:
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