Modulation of dopaminergic cell in Ventral Tegmental Area by Orexin

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Abstract:
Hypocretin 1 and 2 (HCRT1 and 2), also known as Orexin A and B (OXA and OXB), are neuropeptides produced by the lateral hypothalamus, with a highly conserved function and structure among mammalian species. Their receptors, Hcrt-r1 and -r2, respectively, are localized at postsynaptic level and bind both HCRTs with different affinity.
OX neurons connections with cortical and subcortical nuclei allow the integration of different homeostatic signals in order to modulate different physiological functions. One of the main functions concerns the regulation of the sleep-wake cycle, and dysfunctions of OX system causes sleep related disorders, as narcolepsy.
Narcolepsy is a neurological disorder with onset during adolescence and characterized by sudden sleep attacks during awake state and the inability to maintain for long period the vigilance state. It can be associated with cataplexy, i.e. the sudden weakening of muscle tone. It has been demonstrated that narcolepsy is characterized by OX neurons degeneration, as these neurons are absent in human narcoleptic brain (post mortem studies). Current animal models are based on knock out of OX and OXr genes and all of them show the human narcolepsy phenotype. Because of the key role of OX and OXr, therapies used them as targets to control narcolepsy.
One of the implicated area within the OX circuit is the ventral tegmental area (VTA), also involved in reward networks because of the presence of dopaminergic neurons. Interestingly, in animal models, activation of VTA by means of food presentation seems to be the trigger for cataplexy, while antagonists of dopaminergic receptor D2 alleviate the cataplexy symptoms. Despite these anatomical and functional evidences, the role of VTA in OX circuit and in the pathological mechanisms of narcolepsy is still matter of debate.
The aim of the work here presented was to shed light in the modulation of dopaminergic neurons of VTA by OXA and OXB, in physiological condition.
We carried out a patch-clamp study in VTA dissociated cells from wild type mice. We recorded the spontaneous activity of cells in cell-attached configuration in control condition and during and after application of dopamine, OXA and OXB. Our results show that both OXA and OXB modulate VTA dopaminergic cells and represent the starting point for the study of pathological changes in narcolepsy. The study in narcolepsy animal model is planned and it will add a piece of the complex puzzle of the pathological mechanisms of narcolepsy, as well as suggest how to develop new therapies based on new targets.