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Dopamine and action potential generation in the axon initial segment

Marco Canepari^{1,2,3}

¹Univ. Grenoble Alpes, CNRS, LIPhy, F-38000 Grenoble, France. ²Laboratories of Excellence, Ion Channel Science and Therapeutics, France. ³Institut National de la Santé et Recherche Médicale, France.

Dopamine is one of the principal neuromodulators in the brain acting on two large families of receptors, namely D1-like and D2-like. It is involved in several important cognitive and motor functions within different brain areas and it is strongly implicated in rewarding and addiction behaviours. In the medial entorhinal cortex (MEC), dopamine is believed to play a crucial role in the spatial cognition functions performed by this area of the brain (Hafting *et al.*, 2005). In particular, type-2 dopamine receptors (D2Rs) appear to be involved in spatial cognition (Mehta *et al.*, 2001) and stellate cells in the MEC contain high levels of D2Rs. Stellate cells in layer II of the MEC are classified as “grid cells” as they provide spatial information to the animal by spanning the environment. The axons of these neurons innervate the hippocampus forming excitatory synapses. Hence, the physiological pathway triggered by D2R activation in MEC stellate cells is likely fundamental for spatial cognition.

A recently published article by Jin *et al.* (2019) reports novel important findings on the role of dopamine (and in particular of D2Rs) in excitability of stellate cells of the MEC. Dopamine receptors are G-protein coupled receptors (GPCRs) which can regulate the biophysical properties of ion channels and therefore the generation and propagation of the action potential (AP). In this study, the authors first demonstrate that MEC stellate cells direct activation of D2Rs by exogenous application of the agonist bromocriptine, as well as physiological activation of D2Rs by optical stimulation of ChR2 expressed in dopaminergic afferents reduce intrinsic excitability by increasing the threshold for activation of APs. These effects were exclusively mediated by those D2Rs expressed in the stellate cell axon initial segment (AIS). Then, the authors show that the block of T-type voltage-gated Ca^{2+} channels (VGCCs) also increases AP threshold preventing the effect of bromocriptine, while D2Rs activation shifts the activation curve of T-type VGCCs in the more positive direction. Finally, while D2Rs and the T-type VGCC subtype Cav3.2 seem to co-localise in the stellate cell AIS, the authors report evidence that the interaction between D2Rs and T-type channels is regulated by protein kinase PKA. The results reported in this study lead to a schematic explanation of the process illustrated in Figure 1. Dopaminergic fibers, arising from the ventral tegmental area and substantia nigra pars compacta (SNc), innervate the MEC and release dopamine that activates D2Rs in the stellate cell AIS. This GPCR acts on T-type VGCCs *via* a PKA process by shifting the activation profile towards more positive values and, therefore, inhibiting these excitatory channels. This mechanism increases the AP activation threshold and, consequently, decreases cell excitability. This process is also prevented in the presence of high concentrations of the Ca^{2+} chelator BAPTA, but whether this Ca^{2+} dependence arises at the level of the Ca^{2+} influx or, more generally, at the level of the Ca^{2+} homeostasis is still unknown.

Several GPCRs are expressed in the AIS of neurons and this localisation suggests that their function is at the level of AP generation, a phenomenon produced by the synergistic activation of diverse ion channels. This effect is often referred as “intrinsic neuronal plasticity” of the AP. Thus, the functional regulation of ion channels in the AIS is not peculiar of dopamine receptors. For instance, in another study, it was shown that serotonin acts in the AIS of turtle motoneurons to inhibit voltage-gated Na^+ channels (Cotel *et al.*, 2013), in a manner resembling the regulation of T-type VGCCs by dopamine in the stellate cell AIS. In the case of dopamine, the selective activation of one or the other receptor family (D1-like or D2-like) may lead to an opposite effect like in the case of the axon of pyramidal neurons in prefrontal cortex, where dopamine regulates in two ways the activation of voltage-gated K^+ channels (Yang *et al.*, 2013). In a general manner, the specific activation of a GPCR in the AIS may play a crucial role in the higher function performed by a specific area of the central nervous system by participating to the synergistic system composed by different ion channels that generates the AP. In the case of dopamine, the mechanisms characterised in the present study are involved in MEC stellate cell information processing, may contribute to spatial cognition and may possibly occur in other hippocampal and cortical regions innervated by dopaminergic fibers.

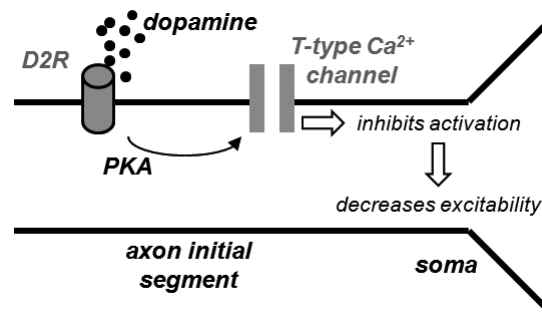


Figure 1. Dopamine affect in the MEC stellate cell AIS

Dopamine activates D2Rs that shifts the activation curve of T-type VGCCs in the more positive direction inhibiting this channels and decreasing neuronal excitability. This interaction is regulated by PKA.

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