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Insights into the inhibitory effect of Ca^{2+} on protein kinase A from molecular dynamics simulations.

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Abstract: Protein kinases are an important family of enzymes that govern many signaling processes within cells by transferring a phosphoryl group from an ATP molecule onto a substrate protein. cAMP-dependent protein kinase, also called protein kinase A (PKA), is one of the most well-studied protein kinases, and because of the high conservation of the protein kinase family, it serves as a model for all protein kinases. Mg^{2+} , as the most abundant divalent metal ion in the cell, is believed to be the favored coordinating ion for kinases, however it has been proven experimentally that other divalent metals such as Ca^{2+} can also promote the phosphoryl transfer but at much lower rates.

We observed, through preliminary molecular dynamics simulations (MDs), that Ca^{2+} tends to increase the mobility of the protein substrate and reduce the mobility of the phosphorylated substrate in PKA; thereby corroborating experimental observations about a “trapping effect” and consequently an inhibitory effect produced by Ca^{2+} . This information is expected to be valuable for the understanding of the catalytic mechanisms in protein kinases which could lead to the design of more potent inhibitors as well as to understand a possible regulation mechanism exerted by Ca^{2+} on kinases.

Conflicts of Interest

The authors declare no conflict of interest.