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Partitioning of Caffeine in Lipid Bilayers Reduces Membrane Fluidity and Increases Membrane Thickness

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Caffeine is the most common adjuvant in drug "cocktails"; however, the mechanisms by which the molecule elicits its adjuvant effects remain unknown. The prevalence of membrane mediated drug-lipid interactions for amphiphilic molecules, such as caffeine, is indisputable through membrane partitioning, bioenergetics, and structure. Here, we characterized caffeine's interactions with cell membranes with respect to hydration with time-resolved X-ray diffraction and Molecular Dynamics simulations [1].

Evidence from both simulation and experiment suggest that caffeine localizes within the head-tail interface of lipid bilayers and increases the thickness of the membrane. By attracting water molecules from neighboring lipid molecules, the partitioning of caffeine leads to the formation of "water pockets", i.e., a local increase of water density in the head-tail interface. Through this mechanism, caffeine leads to an overall decrease of the gauche defect density in the membranes and an increase of membrane thickness, indicating a loss of membrane fluidity. This provides a mechanism by which caffeine can inhibit drug metabolizing enzymes, such as cytochrome P450, which in turn would increase the bioavailability of primary drugs in active-form.

[1] **A Khondker**, A Dhaliwal, RJ Alsop, J Tang, M. Backholm, AC Shi, MC Rheinstädter. Phys. Chem. Chem. Phys., 2017, Advance Article, DOI: 10.1039/C6CP08104E

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