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The Lipid Bilayer Provides a Site for Cortisone Crystallization at High Cortisone Concentrations

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Cortisone is an injected anti-inflammatory drug that is used to treat inflammation. Cortisone's mechanism of action involves binding to an intracellular receptor which transduces a biochemical cascade to reduce the production of inflammatory prostaglandins. However, cortisone is known to confer side effects, such as pain, known as a "steroid flare"for which the mechanism is unknown. Using X-ray diffraction of highly oriented, multi lamellar stacks of lipid membranes and molecular dynamics (MD) simulations, we locate the cortisone molecules within the bilayer, quantified its crystallization, and measured the respective insertion dynamics [1].

At low cortisone concentrations, the molecules localize near the glycerol group of the lipid, and decreased membrane width in a dose-dependent manner. The formation of the cortisone crystallites was observed at higher concentrations, which conferred to a cubic lattice. While the cortisone molecules align parallel to the bilayers at low concentrations, they start to penetrate the hydrophobic core at higher concentrations. Trans-membrane crystallites start to nucleate when the membrane thickness has decreased such that cortisone molecules in the different leaflets can find partners from the opposite leaflet. The results manifests to potentiate a mechanism of action for "steroid flares"by forming crystallites in the bilayer, and offers greater understanding of the drug's action.

[1] RJ Alsop, **A Khondker**, JS Hub, MC Rheinstädter,. Sci. Rep. 6, 22425 (2016).

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