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Cocaine-induced remodeling of the nuclear lamina and 3D genome organization in neurons?

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Sigma-1 receptor (Sig1R) is an ER and nuclear envelope (NE) membrane protein that binds cocaine and many other psycho-active drugs. While studying dopaminergic neurons, Tsung-Ping Su and colleagues (Tsai et al., 2015) discovered that cocaine enhances Sig1R association with three nuclear lamina proteins (emerin, lamin A/C, BANF1) important for tissue-specific 3D genome organization and chromatin silencing. Their association caused the recruitment and transcriptional repression of a gene (*MOAB1*; monoamine oxidase B) essential for dopamine removal from synapses. We propose to apply concepts and knowledge about nuclear structure and 3D genome architecture in other cell types to neurons, to understand the mechanisms of agonist (cocaine)-dependent Sig1R association with **emerin** (a conserved nuclear membrane protein), **lamin A/C** (nuclear intermediate filament proteins) and **Barrier-to-Autointegration Factor** (BANF1; an epigenetic regulator), which are essentially unstudied in neurons. We hypothesize that cocaine drives changes in the composition or activity of nuclear lamina-associated complexes and remodels chromosome organization to favor addiction. As experts in nuclear lamina and genome biology, we see a multitude of fundamental open questions, including the full composition of Sig1R-dependent 'gene-silencing' complexes in dopaminergic neurons, the extent of genome misregulation, and exciting applications for high-resolution DamID-mapping and 3D imaging of silent versus active DNA in individual dopaminergic neurons in the presence or absence of cocaine.