Reactive Oxygen Species induced in innate immune cells by Methamphetamine impact RNA polymerase binding patterns and facilitate the AP-1-mediated transcription of IL1beta and TNFalpha.

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Methamphetamine (Meth) abuse is a common HIV co-morbidity that has been associated to an aggravated Central Nervous System (CNS) inflammation compared to HIV alone. The inflammatory response in the brain of Meth abusers accentuates HIV- associated neurological disorders. The mechanisms of this aggravation are in part triggered by Dopamine, and in part directly induced by the contact of innate immune cells with the drug. We have proposed that Meth has direct effects on innate immune cells to induce transcription of some inflammatory genes. Here, we used the human innate immune THP1 cell line to demonstrate that the Reactive Oxygen Species (ROS) acutely induced by Meth affects the oxy-reduction environment, and signals changes in the RNA polymerase accumulation pattern genome-wide and in selected gene promoters, impacting the regulation of inflammatory gene transcription. We have focused on two key inflammatory genes for validation, IL1beta and TNF alpha, and determined that Meth increases their transcription by affecting Src kinase and EGFR, towards activating AP-1, in a ROS-dependent, dopamine-independent fashion. Our results provide evidence of an effect of Meth-induced ROS as a signaling factor of epigenetic changes that affect the regulation of inflammatory gene transcription.