Phenothiazines and Phenoxazines: As Electron Transfer Mediators for Ferritin Iron Release

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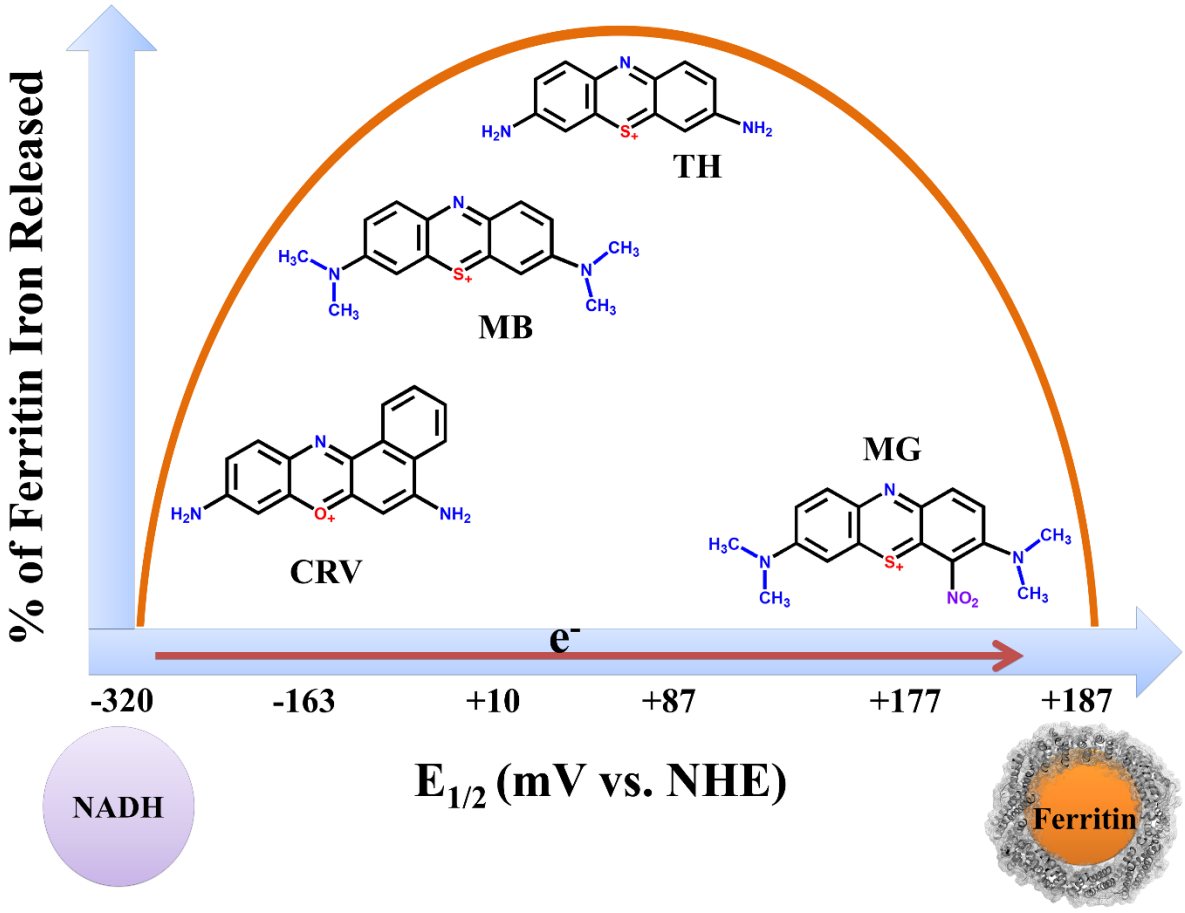
Intracellular ferritin, stores iron as ferrihydrite mineral and releases it for various cellular metabolic activities. Reductive approach, one of the possible mechanisms of iron mobilization from ferritin nanocages, requires electron transfer (ET) from reducing agent(s) to the protein encapsulated iron mineral. *In vitro*, the rate of ET from physiological reducing agent, NADH, to mineralized ferritin is very slow resulting in less amount of iron release. Therefore, medically relevant, phenothiazine and phenoxazine dyes were used as ET mediator to facilitate electron relay and to evaluate their iron releasing ability from ferritin. These dyes have earlier been exploited as ET mediator during electrocatalysis and in the treatment of methemoglobinemia. In comparison to neutral pH, acidic pH altered $E_{1/2}$ and protein conformation leading to enhanced iron mobilization whereas dissolved O_2 and photosensitizing effect of dyes were found to have negligible impact. In analogy to *in vitro*, the acidic environment of the lysosome may bring similar changes in the reducing agents/dye mediators/ferritin to facilitate iron release process *in vivo*. Following Marcus theory, our current observations suggests that the dyes with $E_{1/2}$ values well separated from that of the reducing agents and the ferritin mineral can be exploited to facilitate iron release during iron overload condition. [Dalton Trans., (2019), DOI: 10.1039/c8dt04383c.]



Redox active phenthiazine and phenoxazine dyes facilitate ferritin iron release by acting as electron transfer (ET) mediators following Marcus theory.