Clioquinol changes the expression profiles and redox states of proteins involved in copper/zinc homeostasis

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Clioquinol, extensively used as an amebicide to treat indigestion and diarrhea in the mid-1900s, was withdrawn from the market due to an increase in the incidence of subacute myelo-optic neuropathy (SMON). Yet, the pathogenesis of SMON has not been fully elucidated. Since clioquinol is known as a chelator and ionophore of copper and zinc ions, we focused on proteins involved in homeostasis of these metal ions. A global analysis on human neuroblastoma cells demonstrated that among 4 isoforms of metallothionein (MT), a family of metal-binding proteins, 7 subclasses of MT -1 and MT-2A were remarkably up-regulated by clioquinol. Clioquinol-induced up-regulation of SLC30A1 (zinc exporter ZNT1) was further verified by quantitative PCR. Up-regulation of these proteins suggested that clioquinol activated metal regulatory transcription factor 1 (MTF1)-dependent transcription. We alsoexamined antioxidant 1 (ATOX1), a copper chaperone which has a redox-sensitive metal binding motif and is known to promote neuronal survival. Monitoring the redox state of ATOX1 showed clioquinol-induced thiol oxidization, possibly resulting in the inactivation of ATOX1. Collectively, dyshomeostasis of copper and zinc may be involved in the neurotoxicity of clioquinol.