Oxidative stress has been pointed as an important phenomenon related to metal-induced neurotoxicity. Particularly important, both methylmercury and manganese present pro-oxidative properties, which are related, at least in part, to their neurotoxic effects. However, the whole molecular mechanisms involved with methylmercury- and manganese-induced neuronal oxidative damage are still elusive. We investigated the involvement of the glutathione antioxidant system in the neurotoxicity elicited by methylmercury and manganese compounds in cultured cerebellar granule neurons. Either methylmercury or manganese II chloride induced neuronal death at 3E-7 M and 1.8E-5 M after 5 days of treatment, respectively. At time/concentrations that preceded neuronal death, manganese chloride, but not methylmercury, induced a significant increase in the neuronal glutathione levels. Ascorbic acid and lactate, but not probucol and trolox, prevented manganese-induced neuronal toxicity. Before neuronal death, methylmercury did change neither glutathione levels nor glutathione reductase activity. Conversely, a significant decrease in glutathione peroxidase was observed before neuronal death in methylmercury-exposed neurons (5 div; 300 nM). In close agreement with this observation, methylmercury increased isoprostane levels and the antioxidants ascorbic acid, trolox and probucol prevented methylmercury-induced neuronal death at 7 div. However, only probucol prevented methylmercury-induced lipid peroxidation and inhibition of glutathione peroxidase activity, rendering it a promising molecule for pharmacologic studies on methylmercury neurotoxicity. Taken together, the presented results indicate that methylmercury and manganese chloride induces neuronal oxidative damage by different pathways, where the selenoprotein glutathione peroxidase appears to be an important initial target involved in methylmercury-induced neuronal death.