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Nitric oxide triggers the toxicity due to glutathione depletion in midbrain cultures through 12-lipoxygenase.

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Glutathione (GSH) depletion is the earliest biochemical alteration shown to date in brains of **Parkinson's** disease patients. However, data from animal models show that GSH depletion by itself is not sufficient to induce nigral degeneration. We have previously shown that non-toxic inhibition of GSH synthesis with l-buthionine-(S,R)-sulfoximine in primary midbrain cultures transforms a nitric oxide (NO) neurotrophic effect, selective for dopamine neurons, into a toxic effect with participation of guanylate cyclase (GC) and cGMP-dependent protein kinase (PKG) (Canals, S., Casarejos, M. J., de Bernardo, S., Rodriguez-Martin, E., and Mena, M. A. (2001) J. Neurochem. 79, 1183-1195). Here we demonstrate that arachidonic acid (AA) metabolism through the 12-lipoxygenase (12-LOX) pathway is also central for this GSH-NO interaction. LOX inhibitors (nordihydroguaiaretic acid and baicalein), but not cyclooxygenase (indomethacin) or epoxygenase (clotrimazole) ones, prevent cell death in the culture, even when added 10 h after NO treatment. Furthermore, the addition of AA to GSH-depleted cultures precipitates a cell death process that is indistinguishable from that initiated by NO in its morphology, time course, and 12-LOX, GC, and PKG dependence. The first AA metabolite through the 12-LOX enzyme, 12-hydroperoxyeicosatetraenoic acid, induces cell death in the culture, and its toxicity is greatly enhanced by GSH depletion. In addition we show that if GSH synthesis inhibition persists for up to 4 days without any additional treatment, it will induce a cell death process that also depends on 12-LOX, GC, and PKG activation. In this study, therefore, we show that the signaling pathway AA/12-LOX/12-HPETE/GC/PKG may be important in several pathologies in which GSH decrease has been documented, such as Parkinson's disease. **The potentiating effect of NO over such a signaling pathway may be of relevance as part of the cascade of events leading to and sustaining nerve cell death.**

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