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Response to Comment on “S-Nitrosylation of Parkin Regulates Ubiquitination and Compromises Parkin’s Protective Function”

Our finding that parkin, a ubiquitin E3 ligase, can be selectively S-nitrosylated by nitric oxide (NO) (1) was later confirmed by Yao *et al.* (2) and suggests a common pathogenic pathway in familial and idiopathic Parkinson’s disease (PD). We found that nitrosylation of parkin selectively inhibits parkin’s E3 ligase activity and hence compromises its protective function (1). Yao *et al.* also reported that parkin can be S-nitrosylated (2), but in addition they found a biphasic effect of S-nitrosylation on parkin’s E3 ligase activity: They observed an initial increase followed by a decrease in E3 ligase activity after exposure to the NO donor nitrosocysteine. In further studies carried

out in our laboratory, we too find that parkin S-nitrosylation enhances its E3 ligase activity at earlier time points but inhibits its E3 ligase activity at later time points (Fig. 1), even when the assays are performed at a more physiological oxygen concentration of 5%. Thus, the enhancement of parkin’s E3 ligase activity by S-nitrosylation appears to be an important mechanism by which parkin’s function is regulated. It is conceivable that the multiple sites of cysteine S-nitrosylation of parkin coordinately regulates its activity (1).

It is notable that NO has a biphasic effect on the E3 ligase activity of parkin. Based on these results, Lipton *et al.* (3) propose that the initial transient increase of parkin E3 ligase activity might explain the formation of Lewy bodies in sporadic PD. We suspect that this biphasic regulation plays a more important role in regulating the physiologic E3 ligase activity of parkin—helping to fine tune and regulate the E3 ligase activity of parkin and the ubiquitination of its substrates, much in the same way that phosphorylation and dephosphorylation can regulate the activity of a variety of enzymes. Indeed, in our original report we showed evidence that parkin is S-nitrosylated under normal

nonpathological conditions (1). Although it is tempting to speculate that the enhancement of parkin’s E3 ligase activity leads to Lewy-body formation, we have reservations about this hypothesis. In particular, we showed that there are significant pathologically elevated indices of S-nitrosylation in PD and related disorders (1). Because these disorders are chronic, progressive neurodegenerative disorders, it is likely that the sustained chronic elevation of nitrosative stress leads to an overall decrease in the E3-ligase activity of parkin. The notion that the transient increase of parkin’s E3 ligase activity can subsequently lead to the formation of Lewy bodies and contribute to the pathogenesis of PD is debatable. In particular, whether the transient increase of parkin’s E3 ligase activity is sufficient to increase the production of ubiquitinated inclusion bodies will need to be addressed. In contrast, genetic findings in PD patients suggest that haploinsufficiency of parkin might represent an important risk factor in the development of PD (4, 5). Thus, nitrosative stress probably contributes more to the pathogenesis of idiopathic PD through chronic inhibition of parkin’s E3 ligase activity and the subsequent compromise of parkin’s neuroprotective function.

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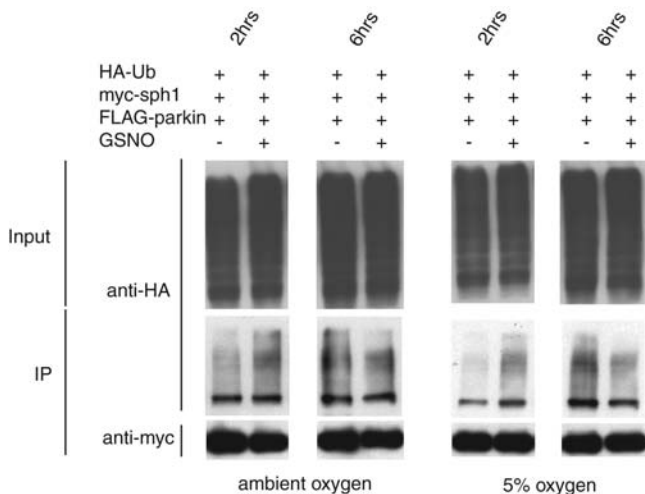


Fig. 1. NO has a biphasic effect on the E3 ligase activity of parkin at ambient and 5% oxygen. Human embryonic kidney (HEK) 293 cells transfected with myc-tagged synphilin-1, FLAG-tagged parkin, and hemagglutinin (HA)-tagged ubiquitin were treated with S-nitrosoglutathione (GSNO) for 2 and 6 hours. S-nitrosylation of parkin enhances its E3 ligase activity at 2 hours but inhibits its activity at 6 hours in ubiquitinating synphilin-1. IP, immunoprecipitation.