Effects of volatile general anesthetics in fly models of mitochondrial disease

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Background/Introduction: Animals harboring mutations in Complex I of the mitochondrial electron transport chain (mETC) display behavioral sensitivity to volatile general anesthetics (VGAs) and may be at increased risk of VGA-induced deleterious collateral effects. We found that mutations in the nuclearly-encoded Complex I gene *ND23* in fruit flies (*Drosophila melanogaster)* also confer behavioral sensitivity to VGAs. The ND23 subunit is the fly ortholog of mammalian NDUFS8. Moreover, we found that exposure of *ND23* mutant flies to isoflurane, but not sevoflurane, caused lethality and that lethality was suppressed by hypoxia (5% O_2) and enhanced by hyperoxia (75% O_2). In the present study, we performed a parallel analysis of the mitochondrially-encoded ND2 subunit of Complex I to determine the extent to which different components of Complex I contribute to deleterious collateral effects of VGAs and to establish a genetically-tractable system to investigate the mechanisms underlying deleterious collateral effects of VGAs.

Methods: Flies of a particular age range were exposed to behaviorally equivalent doses of isoflurane (2%) or sevoflurane (3.5%) in 21% or 75% O_2 for two hours using a custom-made Serial Anesthesia Array (SAA) consisting of agent-specific anesthetic vaporizers, flow meters, and a serial array of anesthetizing positions. Following exposure, flies were incubated under standard culturing conditions and the percent mortality was determined after 24 hours.

Results: As previously observed, isoflurane in normoxia (21% O_2) increased mortality of *ND23* mutant flies relative to unexposed *ND23* mutant flies, but sevoflurane in normoxia did not (unexposed: 5.40 ± 5.01%, isoflurane: 34.45 ± 19.43%, and sevoflurane: 8.04 ± 3.74%). Hyperoxia (75% O_2) further increased mortality from isoflurane exposure to 90.19 ± 11.45%, but hyperoxia did not affect mortality from sevoflurane exposure (3.71 ± 1.89%). Similarly, exposure of *ND2* mutant flies to isoflurane in normoxia increased mortality from 21.89 ± 8.51% to 56.63 ± 12.93 %, and isoflurane in hyperoxia further increased mortality to 99.74 ± 0.64%. In contrast *ND2* mutants deviated from *ND23* mutants in that sevoflurane in hyperoxia increased mortality to 68.21 ± 11.26%, relative to 29.39 ± 8.89% in normoxia.

Conclusions: Mutations in both nuclearly- and mitochondrially-encoded subunits of mETC Complex I increase susceptibility to isoflurane toxicity in flies. However, the mutants differed in their susceptibility to sevoflurane toxicity in hyperoxia. These data indicate that mutations in different Complex I subunits confer VGA-specific susceptibility to toxicity. Using genetic approaches available in flies, we are now in a position to understand the mechanisms underlying vulnerability to VGA-induced toxicity in mitochondrial mutants.