

## CORRESPONDENCE

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## Sevoflurane MAC and Cerebellar Cyclic GMP

*To the Editor:*—The article by Ichinose *et al.*<sup>1</sup> was interesting and enlightening. The sevoflurane minimum alveolar concentration (MAC) reduction effect, in a dose-dependent manner, by acute administration of the neuronal nitric oxide synthase (NOS) inhibitor, 7-nitroindazole (7-NI), is consistent with our previous findings.<sup>2,3</sup> This suggests a role for the nitric oxide signaling pathway in MAC reduction and in the mechanisms mediating consciousness. The additional observation by the authors that MAC of sevoflurane was not reduced in mice after long-term administration of 7-NI is in agreement with other studies.<sup>4,5</sup> However, we would like to address some concerns regarding the interpretation of their data. In their conclusion and implied by their title, Ichinose *et al.*<sup>1</sup> state the possibility that sevoflurane MAC reduction, during long-term administration of 7-NI (= 3 days), was not mediated through the nitric oxide/soluble guanylate cyclase-cyclic guanosine monophosphate (cGMP) pathway. This was based on the fact that long-term administration of 7-NI did not reduce sevoflurane MAC, despite a reduction in cGMP production. The authors cannot speculate on the role of cGMP in the mechanism of sevoflurane MAC reduction when they did not show any MAC reduction during long-term administration of 7-NI. In contrast, the sevoflurane MAC reduction obtained after acute administration of 7-NI suggests a correlation between sevoflurane MAC reduction and decrease in cGMP production. The fact that long-term administration of 7-NI failed to reduce sevoflurane MAC could be related to cGMP-independent compensatory mechanisms that mediate nociception (as suggested by the authors) or excitatory cGMP-independent compensatory mechanisms that stimulate consciousness centers, or both. Indeed, there is a precedent for heterologous compensation of nitric oxide inhibitor-induced MAC reduction when the inhibitor is administered for prolonged periods<sup>5</sup> and in studies performed in neuronal nitric oxide synthase knockout mice.<sup>4,6</sup>

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*In Reply:*—I thank Drs. Haddad, Johns, and Pajewski for their interest and valuable comments regarding our recent article.<sup>1</sup> I have to admit that our speculation regarding the role of cyclic guanosine monophosphate (cGMP) in the mechanism of sevoflurane minimum alveolar concentration (MAC) reduction is based on rather weak evidence. I also agree with Haddad *et al.* regarding the possible development of compensatory mechanisms as we described in our discussion. However, we would like to point out that, although we found a correlation between the reduction of cGMP and sevoflurane MAC after acute 7-NI, there was a marked difference in the magnitude of reduc-

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tion of the two parameters. Together with the dissociation of the two parameters after long-term 7-NI administration, these observations may suggest that the relation between cGMP and MAC is not linear. It is conceivable that only a small amount of nitric oxide or cGMP, or both, is necessary to maintain normal nociception. If this is the case, variation of nitric oxide synthase (NOS) activity or cGMP concentrations, or both, in the brain may not closely correlate with MAC of volatile anesthetics. I would also like to point out the limitation of the studies of our own<sup>1</sup> and others<sup>2</sup> that tested the effects of NOS inhibitors on anesthetic potencies and NOS activities. In two studies in which cGMP