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Persistent alteration in behavioural reactivity to a mild social stressor in rhesus monkeys repeatedly exposed to sevoflurane in infancy

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This article is accompanied by an editorial: Monkey business: the importance of mounting behavioural evidence for anaesthesia-induced developmental neurotoxicity by V. Jevtovic-Todorovic, *Br J Anesth* 2018:120:617–619, doi: 10.1016/j.bja.2018.02.001.

Abstract

Background: Socio-emotional development is the expression and management of emotions, which in non-human primates can be examined using responses toward increasing levels of threat. Damage to the limbic system alters socio-emotional development in primates. Thus, neuronal and glial cell loss caused by exposure to general anaesthesia early in infancy might also impact socio-emotional development. We recently reported that repeated sevoflurane exposure in the first month of life alters emotional behaviours at 6 months of age and impairs visual recognition memory after the first year of life in rhesus monkeys. The present study evaluated socio-emotional behaviour at 1 and 2 yr of age in those same monkeys to determine the persistence of altered emotional behaviour.

Methods: Rhesus monkeys of both sexes were exposed to sevoflurane anaesthesia three times for 4 h each time in the first 6 weeks of life. At 1 and 2 yr of age, they were tested on the human intruder task, a well-established mild acute social stressor.

Results: Monkeys exposed to sevoflurane as infants exhibited normal fear and hostile responses, but exaggerated self-directed (displacement) behaviours, a general indicator of stress and anxiety in non-human primates.

Conclusions: Early repeated sevoflurane exposure in infant non-human primates results in an anxious phenotype that was first detected at 6 months, and persists for at least 2 yr of age. This is the first demonstration of such a prolonged impact of early anaesthesia exposure on emotional reactivity.

Keywords: anaesthetic neurotoxicity; cognitive development; general anaesthesia

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Editor's key points

- The long-term impact of early, repeated exposure to anaesthesia on socio-emotional behaviour is unknown.
- In a follow-up study of non-human primates exposed thrice to inhaled sevoflurane as infants, the human intruder test was used to assess socio-emotional behaviours at 1 and 2 yr of age.
- Monkeys exposed to sevoflurane as infants had exaggerated displacement behaviours, an indicator of stress and anxiety in non-human primates, up to 2 yr after exposure.
- Repeated exposure to sevoflurane as infants can have long-term effects on socio-emotional behaviours in rhesus monkeys.

A number of epidemiological studies have reported increased incidence of neurocognitive abnormalities after paediatric surgery and anaesthesia, particularly in children with repeated or prolonged exposure to anaesthesia.[1–10] Studies in animal models, both rodents and non-human primates, allow isolation of the effect of general anaesthesia from that of surgery. Exposure to general anaesthesia alone in infant rodents or monkeys causes programmed cell death (apoptosis) of neuronal and glial cells, and long-term alterations in cognitive and socio-emotional behaviour.[11–15]

We are studying cognitive and socio-emotional development in rhesus monkeys exposed to sevoflurane inhalation anaesthesia three times in infancy, in comparison with a control group in which infants were briefly separated from their mothers at the same time points. Our model focuses on repeated exposure because this is most reliably associated with neurocognitive impairment in human epidemiological studies.[1–4] Indeed, recent prospective and ambidirectional studies in humans have suggested that single, relatively brief (on the order of 1–2 h) exposures to general anaesthesia in humans do not have substantial impact on neurocognitive development, at least with the measures used and at the time points tested.[16,17] We have previously reported increased displacement (anxiety) behaviour at 6 months of age,[14] and delayed-onset mild visual memory deficits that emerge at 2 yr of age[18] in rhesus monkeys repeatedly exposed to sevoflurane as infants.

Here, we re-evaluated emotional reactivity in these same monkeys at later developmental time points where memory impairments were evident. At 1 and 2 yr of age, sevoflurane-exposed monkeys exhibited increased self-directed (displacement) behaviours that were stable between the two assessments 1 yr apart. In humans and non-human primates, displacement behaviours are patterns of movements focused on one's own body, such as self-touching, scratching, and self-grooming. Displacement behaviours reflect general anxiety, as they are increased by anxiogenic events, catecholamines, or glucocorticoids, and decreased by anxiolytics[19,20] Therefore, repeated anaesthesia exposure early in life seems to result in an anxious phenotype characterised by different displacement behaviours during infancy and adolescence, specifically increased frequency of anxiety behaviours (e.g. scratching, yawning) during infancy, and increased duration of self-directed behaviours (e.g. self-grooming) as juveniles.

Methods

All animal procedures were approved by the Yerkes National Primate Research Center and the Emory University Institutional Animal Care and Use Committee, and were conducted in full compliance with United States Public Health Service Policy on Humane Care and Use of Laboratory Animals. Subject descriptions and anaesthetic procedures have been published.[14] Briefly, 20 newborn rhesus monkeys of Indian origin (*Macaca mulatta*) were born in two cohorts in the breeding colony at the Yerkes National Primate Research Center field station. In the first cohort, six females and four males were born in the 2012 birth season, and in the second, four females and six males were born in 2013. All infants were delivered vaginally without veterinary intervention in their natal group compounds. Infants were born to middle-ranking dams and were housed in large social groups of 50–100 individuals comprising several family groups. Infants were assigned as they were born and with consideration to balancing for sex and weight to either the control group or the anaesthesia group. A power analysis before beginning the study indicated that 10 animals per group would give 80% power to detect an effect size of partial eta squared (η_p^2)=0.25 in a comparison of group means,[14] hypothesising cognitive impairment after early anaesthesia exposure. That effect size and number of subjects is also reasonable for detecting group differences in

Table 1 Physiological measures during sevoflurane exposure. P6–10, postnatal days 6–10. Reprinted with modifications from Raper and colleagues,[14] with permission from the publisher, American Society of Anesthesiologists Inc

	First anaesthetic (P6–10)	Second anaesthetic (14 days after first)	Third anaesthetic (28 days after first)
	Mean (SD)		
End-tidal carbon dioxide (kPa)	5.01 (0.47)	5.30 (0.42)	5.03 (0.24)
Respiration rate (bpm)	52 (1)	45 (8)	43 (10)
Oxygen saturation of haemoglobin (%)	97 (2)	97 (2)	98 (1)
Pulse rate (beats min^{-1})	152 (22)	159 (15)	160 (19)
Rectal temperature (°C)	37.1 (0.4)	37.2 (0.3)	37.1 (0.3)
Inspired sevoflurane (%)	2.48 (0.17)	2.61 (0.16)	2.66 (0.27)
Expired sevoflurane (%)	2.46 (0.15)	2.59 (0.15)	2.64 (0.28)
Blood pressure (mm Hg)	56 (20)	52 (18)	55 (14)
Blood pH	7.38 (0.03)	7.39 (0.05)	7.41 (0.03)