A poisoned chalice: the heritage of parental anaesthesia exposure

Vutskits, Laszlo; Sall, J W; Jevtovic-Todorovic, V

How to cite

VUTSKITS, Laszlo, SALL, J W, JEVTOVIC-TODOROVIC, V. A poisoned chalice: the heritage of parental anaesthesia exposure. In: British Journal of Anaesthesia, 2018, vol. 121, n° 2, p. 337–339. doi: 10.1016/j.bja.2018.05.013

This publication URL: https://archive-ouverte.unige.ch/unige:128648
Publication DOI: 10.1016/j.bja.2018.05.013

Declaration of interest

G.S.M. has served as a consultant and speaker for Merck.

Funding

None declared.

References

1. Rodney G, Ball DR. Not just monitoring; a strategy for managing neuromuscular blockade. *Anaesthesia* 2015; **70**: 1105–18
2. Brull SJ, Prielipp RC. Reversal of neuromuscular blockade: "identification friend or foe". *Anesthesiology* 2015; **122**: 1183–5
3. Naguib M, Kopman AF, Lien CA, Hunter JM, Lopez A, Brull SJ. A survey of current neuromuscular practice in the United States and Europe. *Anesth Analg* 2010; **111**: 110–9
4. Thilen SR, Ng IC, Cain KC, Treggiari MM, Bhananker SM. Management of rocuronium neuromuscular blockusing a protocol for qualitative monitoring andreversal with neostigmine. *Br J Anaesth* 2018; **121**: 367–77
5. Murphy GS, Szokol JW, Marymont JH, et al. Intraoperative acceleromyographic monitoring reduces the risk of residual neuromuscular blockade and adverse respiratory events in the postanesthesia care unit. *Anesthesiology* 2008; **109**: 389–98
6. Hristovska AM, Duch P, Allingstrup M, Afshari A. Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults. *Cochrane Database Syst Rev* 2017; **8**. CD012763
7. Brull SJ, Kopman AF. Current status of neuromuscular reversal and monitoring: challenges and opportunities. *Anesthesiology* 2017; **126**: 173–90
8. Brull SJ, Murphy GS. Residual neuromuscular block: lessons unlearned. Part II: methods to reduce the risk of residual weakness. *Anesth Analg* 2010; **111**: 129–40
9. Bronsert MR, Henderson WG, Monk TG, et al. Intermediate-acting nondepolarizing neuromuscular blocking agents and risk of postoperative 30-day morbidity and mortality, and long-term survival. *Anesth Analg* 2017; **124**: 1476–83
10. Bulka CM, Terekhov MA, Martin BJ, Dmochowski RR, Hayes RM, Ehrenfeld JM. Nondepolarizing neuromuscular blocking agents, reversal, and risk of postoperative pneumonia. *Anesthesiology* 2016; **125**: 647–55
11. Arbous MS, Meursing AE, van Kleef JW, et al. Impact of anesthesia management characteristics on severe morbidity and mortality. *Anesthesiology* 2005; **102**: 257–68
12. Errando CL, Garutti I, Mazzinari G, Díaz-Cambronero Ó, Bebawy JF. Residual neuromuscular blockade in the postanesthesia care unit: observational cross-sectional study of a multicenter cohort. *Minerva Anesthesiol* 2016; **82**: 1267–77
13. Hunter JM. Reversal of residual neuromuscular block: complications associated with perioperative management of muscle relaxation. *Br J Anaesth* 2017; **119**: i53–62
14. Kopman AF. Normalization of the acceleromyographic train-of-four fade ratio. *Acta Anaesthesiol Scand* 2005; **49**: 1575–6
15. Schreiber JU, Mucha E, Fuchs-Buder T. Acceleromyography to assess neuromuscular recovery: is calibration before measurement mandatory? *Acta Anaesthesiol Scand* 2011; **55**: 328–31
16. Kim KS, Cheong MA, Lee HJ, Lee JM. Tactile assessment for the reversibility of rocuronium-induced neuromuscular blockade during propofol or sevoflurane anesthesia. *Anesth Analg* 2004; **99**: 1080–5
17. Kirkegaard H, Heier T, Caldwell JE. Efficacy of tactile-guided reversal from cisatracurium-induced neuromuscular block. *Anesthesiology* 2002; **96**: 45–50
18. Kaufhold N, Schaller SJ, Stäuble CG, et al. Sugammadex and neostigmine dose-finding study for reversal of residual neuromuscular block at a train-of-four ratio of 0.2 (SUNDRO20). *Br J Anaesth* 2016; **116**: 233–40
19. Thevathasan T, Shih SL, Safavi KC, et al. Association between intraoperative non-depolarising neuromuscular blocking agent dose and 30-day readmission after abdominal surgery. *Br J Anaesth* 2017; **119**: 595–605

British Journal of Anaesthesia, 121 (2): 337–339 (2018)
doi: 10.1016/j.bja.2018.05.013
Advance Access Publication Date: 7 June 2018

A poisoned chalice: the heritage of parental anaesthesia exposure

L. Vutskits[1,*], J. W. Sall[2] and V. Jevtovic-Todorovic[3]

[1]Department of Anesthesiology, Pharmacology and Intensive Care, University Hospital of Geneva, Geneva, Switzerland, [2]Department of Anesthesia and Perioperative Care, University of California, San Francisco, CA, USA and [3]Department of Anesthesiology, University of Colorado School of Medicine, Aurora, CO, USA

*Corresponding author. E-mail: laszlo.vutskits@unige.ch

DOI of original article: doi: 10.1016/j.bja.2018.04.034.

Parental influence has a huge impact on the emotional and cognitive development of children. Now, an increasing number of studies suggest that this influence may not be limited to early childhood, but can even start well before the conception of the progeny. For example, parental lifetime stress experience, even before pregnancy, can lead to altered offspring stress reactivity along with an increased risk for neuropsychiatric disease.[1] Moreover, recent studies reveal that early life exposure to a variety of chemicals can affect the health of subsequent generations, and that dysregulation of the hypothalamic-pituitary-adrenal stress axis is central to these pathologies.[2] These latter observations are particularly alarming in the context of neonatal and paediatric perioperative care, as general anaesthetics are powerful modulators of neuronal activity and are known to induce a wide variety of morpho-functional effects when administered during critical periods of brain development.[3,4] To further substantiate possible transgenerational effects of early life anaesthesia exposure, rodent experimental data reveal altered learning capabilities after halothane and enflurane exposure in second generation offspring.[5]

In this issue of the *British Journal of Anaesthesia*, Ju and colleagues[6] present interesting new mechanistic insights on how behavioural and cognitive deficits, associated with early life anaesthesia exposure, can be transmitted to following generations. The authors exposed 5-day-old rat pups to sevoflurane for 6 hr, and showed that this treatment paradigm induced lasting behavioural deficits not only in these animals, but also in their male progeny. These sex-specific differences in transgenerational behavioural patterns were correlated with reduced expression of the cation chloride cotransporter KCC2 in the hippocampus and hypothalamus of F1 males from exposed parents. The molecular pathway behind sevoflurane-induced transgenerational sex-specific decrease in KCC2 expression appears to involve epigenetic mechanisms, namely increased deoxyribonucleic acid (DNA) methylation of the KCC2 gene promoter in the sperm of F0 exposed sires.

These observations are of interest as they confirm previously suggested lines of thought and further enhance our understanding of the potentially very long-term effects of early anaesthesia exposures. The first important point is that anaesthetics induce epigenetic modification of the genome, a finding that has been known for some time. The initial focus was on histone modifications, which showed that anaesthetics can modulate histone acetylation and as such may have deleterious effects on transcription of genes crucial for proper synapse formation and cognitive development.[7] The study by Ju and colleagues[6] is an interesting confirmation of early behavioural observations[5] and recently published evidence.[7] Whether the epigenetic changes involve key transcription factors [e.g. cAMP response element-binding (CREB) protein, CREB-binding protein] leading to downregulation of target genes (e.g. brain-derived neurotrophic factor, c-Fos) via histone modification as previously shown, or modulation of the KCC2 expression via modification of DNA methylation as shown in this study, it is increasingly clear that general anaesthetics are powerful epigenetic modulators when administered during critical stages of synaptogenesis. Hence, we are faced with a real possibility that general anaesthetics are not innocuous agents that 'only put children to sleep' but rather formidable modulators of chromatin remodelling and function.

This work by Ju and colleagues[6] confirms and extends previously published reports from several investigators using rodent models of sex-specific differences in behavioural outcome after anaesthesia exposure.[8,9] In nearly all cases, outcomes after anaesthesia exposure follow a pattern seen after neonatal stroke or trauma where males perform worse than females. The mechanism for these sex differences has not been unravelled, and the complex regulation of steroid hormones and conversion of androgens to oestrogen in target organs complicates such studies. However, it is known that the developmental change from GABAergic excitation to inhibition that happens in a region-specific manner occurs earlier in females than males,[10] which could contribute to the sex-specific outcomes reported. The current study extends previous reports of sex differences by showing that anaesthetic exposure itself can alter expression of chloride channels in certain brain regions and that this effect is heritable from exposed male parents to unexposed offspring.

Last but not least, the data provided by Ju and colleagues[6] raise the intriguing possibility that anaesthesia exposure during early postnatal life can interfere with the functional maturation of GABAergic systems from excitatory toward inhibitory effects. A delay in this transition could have important physiological consequences. Indeed, even small changes in the relative balance of excitation and inhibition can markedly alter information processing, and the role of GABA-mediated control of neural plasticity during critical periods of early postnatal life is well-established.[11] The onset of critical period plasticity can be delayed by preventing maturation of the GABAergic system, while the opposite is true when maturation of this system is accelerated pharmacologically using diazepam. In this context, the observation that sevoflurane, a potent positive allosteric modulator of the $GABA_A$ receptor similar to diazepam, prevents rather than accelerates this maturation is intriguing. Pharmacodynamic differences between these drugs could provide a plausible explanation. In line with this possibility, propofol, another positive allosteric modulator of the $GABA_A$ receptor, does not apparently modify KCC2 expression when applied during early postnatal life.[12]

The translational relevance of this study is difficult to judge as it has been difficult to show an effect in first generation of exposed humans. Because of the numerous confounding variables associated with long intergenerational times, along with changes in clinical practice, it would be nearly impossible to evaluate the human relevance with any degree of control. However, this by no means undermines the importance of these fundamental observations that provide further evidence supporting general anaesthetics as powerful modulators of developmental neuroplasticity. Indeed, it should be remembered that clinical outcome is a composite measure. It is the role of basic anaesthesia research to figure out the contributing factors.

Authors' contributions

Conception, writing, and approval of final version: all authors.

Declaration of interest

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

References

1. Rodgers AB, Bale TL. Germ cell origins of posttraumatic stress disorder risk: the transgenerational impact of parental stress experience. *Biol Psychiatry* 2015; **78**: 307–14
2. Xin F, Susiarjo M, Bartolomei MS. Multigenerational and transgenerational effects of endocrine disrupting chemicals: a role for altered epigenetic regulation? *Semin Cell Dev Biol* 2015; **43**: 66–75
3. Vutskits L, Xie Z. Lasting impact of general anaesthesia on the brain: mechanisms and relevance. *Nat Rev Neurosci* 2016; **17**: 705–17
4. Chalon J, Tang CK, Ramanathan S, Eisner M, Katz R, Turndorf H. Exposure to halothane and enflurane affects learning function of murine progeny. *Anesth Analg* 1981; **60**: 794–7
5. Soriano SG, Vutskits L, Jevtovic-Todorovic V, Hemmings HC. Thinking, fast and slow: highlights from the 2016 BJA seminar on anaesthetic neurotoxicity and neuroplasticity. *Br J Anaesth* 2017; **119**: 443–7
6. Ju LS, Yang JJ, Morey T, et al. Role of epigenetic mechanisms in transmitting the effects of neonatal sevoflurane to the next generation of male, but not female, rats. *Br J Anaesth* 2018; **121**: 406–16
7. Dalla Massara L, Osuru HP, Oklopcic A, et al. General anesthesia causes epigenetic histone modulation of c-fos and brain-derived neurotrophic factor, target genes important for neuronal development in the immature rat hippocampus. *Anesthesiology* 2016; **124**: 1311–27
8. Lee BH, Chan JT, Kraeva E, Peterson K, Sall JW. Isoflurane exposure in newborn rats induces long-term cognitive dysfunction in males but not females. *Neuropharmacology* 2014; **83**: 9–17
9. Gonzales EL, Yang SM, Choi CS, et al. Repeated neonatal propofol administration induces sex-dependent long-term impairments on spatial and recognition memory in rats. *Biomol Ther (Seoul)* 2015; **23**: 251–60
10. Nunez JL, McCarthy MM. Resting intracellular calcium concentration, depolarizing gamma-aminobutyric acid and possible role of local estradiol synthesis in the developing male and female hippocampus. *Neuroscience* 2009; **158**: 623–34
11. Hensch TK. Critical period plasticity in local cortical circuits. *Nat Rev Neurosci* 2005; **6**: 877–88
12. Lacoh CM, Bodogan T, Kaila K, Fiumelli H, Vutskits L. General anaesthetics do not impair developmental expression of the KCC2 potassium-chloride cotransporter in neonatal rats during the brain growth spurt. *Br J Anaesth* 2013; **110**: i10–8

British Journal of Anaesthesia, 121 (2): 339–342 (2018)
doi: 10.1016/j.bja.2018.05.061
Advance Access Publication Date: 25 June 2018

Undertreated or overtreated? Opioids for postdelivery analgesia

C. A. Wong[1,*] and T. Girard[2]

[1]Department of Anesthesia, University of Iowa, Iowa City, IA, USA and [2]Department of Anesthesiology, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital of Basel, Basel, Switzerland

*Corresponding author. E-mail: cynthia-wong@uiowa.edu

In 2016, more people in the USA died from opioid overdose than from traffic accidents (42 000 *vs* 37 461), making drug overdose the leading cause of accidental death.[1,2] In the European Union, ~6000 deaths were attributed to opioid overdose; the highest number of deaths occurred in the UK.[3] In both the USA and Europe, the rates of opioid overdose have increased in the past several years. The increase, however, has been much more dramatic in the USA, leading to the declaration of a public health emergency in October 2017.[4]

Why has the USA seen this dramatic increase in opioid overdose deaths? And why are the number of deaths dramatically higher there than in Europe? Among the 2016 US deaths, 40% involved a prescription opioid (average 46 deaths per day); the most common prescription drugs involved in overdose deaths were hydrocodone, oxycodone, and methadone.[1] Opioid consumption per capita is markedly higher in the USA and Canada than in Europe.[5] Physicians in the USA seem more willing to prescribe opioid analgesia (there are several likely reasons for this, including incentives that link reimbursement to patient satisfaction—patient satisfaction has been linked to opioid prescriptions[5]). More directly coupled to anaesthesia care, a contributing factor may relate to differences in the management of acute pain in the USA and Europe, including acute postoperative pain.[5,6] An important solution to this problem is a better understanding of the natural history of pain after operative procedures, and

DOI of original article: doi: 10.1016/j.bja.2018.04.033.