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Anaesthesia, neural activity, and brain development: interneurones in the spotlight

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Developing brain networks are particularly receptive to acquiring certain kinds of information and even need those instructive signals for their continued functional assembly. Information input is commonly translated into neural activity driven primarily by GABAergic and glutamatergic neurotransmission. During critical periods of neural development, the timing and duration of neural activity patterns in maturing brain circuitry sculpt function, and even short interference with physiological activity patterns can trigger long-term functional consequences.[1] In this context, and as anaesthetics are major pharmacological modulators of neural activity, it is not surprising that experimental data in animals convincingly raise the plausibility for persistent behavioural and cognitive alterations after exposure to anaesthetics in early postnatal life.[2] Although the human relevance of these laboratory observations remains debated, manipulating neural activity with general anaesthetics during brain development provides us with an extraordinary experimental tool to study critical-period neural plasticity. Indeed, deciphering molecular, cellular, and network mechanisms underlying the effects of anaesthesia exposure on immature brain networks may provide us with a better understanding of the context-dependent modulation of neural plasticity. In addition to advancing academic knowledge, this line of research may also lead us to develop therapeutics, where general anaesthetics could be used as modulators of pathological plasticity states, an exciting concept that goes beyond the current use of these drugs to provide a rapidly reversibly state of unconsciousness.[3]

In this issue of the *British Journal of Anaesthesia*, Zhou and colleagues[4] provide thought-provoking new information about the long-term impact of early-life anaesthesia exposure on developing neural networks. In line with some previous laboratory observations, the authors first show that repeated (but not single) exposures of neonatal mice to propofol induce long-term behavioural, cognitive, and motor impairments in these animals, and that these functional deficits are associated with a decrease in the number of pyramidal neurones and excitatory synaptic contacts in the cerebral cortex. Administered the unconventional non-competitive gamma-aminobutyric acid type A ($GABA_A$) receptor agonist pentylenetetrazol or the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor agonist CX546 to mice recovering from anaesthesia, they found that these treatments, aimed to accelerate recovery of physiological patterns of neural activity, protected against the long-term effects of propofol exposure. Using a combination of genetic cell labelling methodologies and sophisticated *in vivo* neuronal imaging

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technologies in mice, the authors also investigated the neural circuitry mechanisms underlying these effects. By focusing on the motor cortex several months after repeated propofol exposure, they show that neural activity patterns of both excitatory pyramidal cells and inhibitory interneurones differ from control animals under resting conditions and when performing a motor task. In contrast, no meaningful difference in neural activity patterns was found between control animals and those where recovery from early-life propofol anaesthesia was accompanied by co-administration of either pentylenetetrazol or CX546.

This important experimental study strengthens the growing body of evidence that exposure to general anaesthesia can induce lasting changes in neuronal circuitry, extending the effects of these drugs far beyond the duration of the anaesthetic state. However, the observations of Zhou and colleagues[4] also provide us with new and fascinating mechanistic insights by proposing a role for local inhibitory interneurone networks of the cerebral cortex to drive these long-term effects. Inhibitory interneurones are major determinants of the balance between excitation and inhibition in the cerebral cortex. These highly heterogeneous populations of interneurones are crucial in shaping pyramidal neuronal responses, and thereby cortical output. The authors show that repeated propofol exposure as neonates results in distinctly altered activity patterns of several interneurone types in adult animals. They observed increased activity of vasoactive intestinal peptide-expressing interneurones, which may explain the concomitantly decreased activity of parvalbumin- and somatostatin-positive cortical interneurones. Although the authors did not investigate causality between altered neural activity patterns in interneurones and the activity of pyramidal cells, these observations raise the possibility that the persistent functional deficits observed in several experimental models after exposure to anaesthetics during critical periods of early postnatal development may stem from the effects of these drugs on developing interneurones. The facts that the maturation of cortical interneurones is exquisitely sensitive to cell-extrinsic factors and that pharmacological manipulation of these cells during critical periods of development results in permanently changed function argue support this explanation.[1]

These observations may also have relevance outside the field of anaesthesiology. Indeed, altered inhibitory network function in the cerebral cortex is increasingly proposed as a mechanism to explain neurobehavioural pathologies, such as schizophrenia, autism spectrum, or attention deficit hyperactivity disorders.[5] In this context, the fact that relatively short exposures to propofol in the early neonatal period result in permanently altered activity of inhibitory cortical interneurones makes this experimental model appealing to study the pathological bases of these developmental disorders. Moreover, the findings that accelerating recovery of physiological patterns of neural activity after general anaesthesia protects against the undesirable long-term effects of early-life anaesthesia exposure could give rise to a series of fundamental questions related to modulation of critical-period plasticity. One of the most intriguing questions is whether and how manipulation of neuronal activity by anaesthetics or other approaches at later stages of life can reset network activity and function from 'pathological' to 'physiological' levels. As is often the case with all good research, the study by Zhou and colleagues[4] raises more questions than it answers.

What are the clinical implications of these observations in paediatric anaesthesia practice? The translational relevance of the repeated anaesthesia exposure paradigm remains, at best, difficult to extrapolate to clinical practice. Despite the biological plausibility of developmental anaesthesia neurotoxicity, there is so far no objective human clinical phenotype supporting this possibility.[6,7] Nevertheless, the observations of Zhou and colleagues[4] may guide the hunt for this phenomenon. Functional exploration of human inhibitory neural activity using multimodal imaging studies between control and individuals exposed to anaesthesia in early life may be a promising approach. In the meantime, it is important to note that basic science studies in the field of anaesthesia do not necessarily have direct translational relevance. They do have an important place in exploring basic biological phenomena, and thereby deepening our understanding of the world. The clinical implications, inside or outside the field of anaesthesia, may or may not follow. The sophisticated animal studies of Zhou and colleagues[4] provide an excellent example of this.

Declarations of interest

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