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PERSPECTIVE

Intentional and unintentional impacts of anaesthesia: insights from experiments in pain and injury

The study of brain function in the presence of pain and injury is a rapidly expanding field of experimental research. Clinically, the presence of pain and injury is often accompanied by reports of behavioural change and altered cognition. Even in a highly controlled environment such as the surgical operating theatre postoperative behavioural changes including posttraumatic stress disorder, depression, chronic fatigue, and chronic pain often present in a sub-group of patients (Borsook et al., 2010). The growing recognition of co-morbid behavioural abnormalities in the presence of pain and injury presents an exciting avenue of experimental research into brain function for scientists. To study the brain in the presence of pain and injury raises ethical questions, in particular with regards to the experimental induction of pain and/or injury. One potential avenue is the use of spontaneous and/or naturalistic pain and injury models (Klinck et al., 2017), but such an approach presents a number of logistic complexities that could make it difficult and impractical for many investigators.

A more widely used alternative is surgical manipulation that models pain and/or injury. The use of general anaesthetics to induce unconsciousness and supress sensory perception enabled not only surgery as a form of treatment, but also as a means to perform experimental research. The use of general anaesthetics is often considered safe, and is generally thought to induce a reversible brain state. An important consideration for therapeutic uses and for understanding brain function in an experimental context. However, an issue that arises with the use of general anaesthetics is what if it does not always induce a completely reversible brain state?

There is a lot of apparently conflicting data that offer differing viewpoints on the question of whether general anaesthetics have long-term effects on the adult brain. These differences in data may in part be a result of subtle effects of differences in external conditions and situational factors, in combination with the exposure to general anaesthesia that have an unappreciated, yet lasting impact on adult brain function. Some examples of potential influential factors are different forms of acute stress that may arise during the perioperative period. These include, but are not limited to anxiety, pain, the surgical stress response and the potential neurotoxicity/neuroprotection of anaesthetic agents themselves, all of which are well documented in the clinical setting (Borsook et al., 2010).

Identifying long-term changes in adult human brain function as a result of exposure to general anaesthesia alone, in the absence of a clinical intervention, has not been systematically investigated. However, recent data from the brains of adult rats, support an enduring effect of the inhalational anaesthetic, isoflurane on both brain function and behaviour. Following a two-hour exposure to isoflurane, the study revealed learning deficits that lasted up to seven days and provided electrophysiological and biochemical evidence for altered synaptic plasticity. These effects were detected at a time point where the residual isoflurane concentration was presumed to be negligible (Uchimoto et al., 2014). In addition, similar long-term behavioural alterations have also observed in different species. In mice, a similar 2-hour exposure to isoflurane resulted in impaired attentional behaviours. However, there were no distinct effects on memory function when measured seven days after exposure to the anaesthetic (Yonezaki et al., 2015). Similarly enduring biochemical alterations were observed in the prefrontal cortex of adult rats following a twenty-minute exposure to the inhalational anaesthetic, halothane. Six days after exposure to the anaesthetic, there were large increases in the neurotrophic factor, brain derived neurotrophic factor (BDNF) and its receptor Tropomyosin receptor kinase B (TrkB) mRNA (Kang et al., 2017). It is intriguing that these data show that inhalational anaesthetics alone produce changes in the function of the adult brain and consequently behavioural changes that greatly outlast the duration of anaesthesia. These data suggest that there is a period of time after exposure to an anaesthetic during which the brain may be more susceptible to the influence of external factors, an observation that raises important questions about post-anaesthetic recovery.

A common behavioural change observed after anaesthesia and surgical procedures is postoperative cognitive decline (POCD). POCD comprises a decline in cognitive function that includes impairments in memory, attention and decision-making, that typically resolves within twelve months (Ologunde and Ma, 2011). The causes of POCD are not well understood as it is difficult to separate the effects of anaesthesia, surgery and inflammation on its development. Preclinical studies have shown that exposure to general anaesthesia alone, can result in altered cognitive function in experimental animals. Thus it is not unreasonable to suspect that anaesthetics play a significant role in the development of POCD. Exposure to anaesthetics is known to disrupt synaptic formation and trigger neuroinflammation each of which provide viable mechanisms for altered brain function.

Synapse formation and function underpins neural circuit formation and function and synaptic strength depends critically on the dendritic spines of neurons. In the developing rat brain, it has been shown that general anaesthetics including isoflurane, sevoflurane, and propofol each have the capacity to alter dendritic spine density and morphology (Vutskits and Xie, 2016). In young rodent pups, exposure to isoflurane or propofol during the early stages of development, between postnatal days P5 and P10, resulted in a rapid loss in the number of dendritic spines and synapses throughout the brain. However, in contrast at later postnatal development time points such as P15 or P20, exposure to sevoflurane or propofol resulted in an increase in dendritic spine densities in cortical neurons (Vutskits and Xie, 2016). The effects of general anaesthesics on synaptic formation in mature or aged neuronal circuits, have not been specifically investigated. However, the findings from the developing brain raise the possibility that general anaesthesia may also have lasting effects on neural connectivity in the adult brain and therefore on behavioural outcomes.

Although a 'priming effect' of general anaesthesia on the adult brain has worrying implications. A potential for therapeutic use is also highlighted. Recent studies have reported anti-depressant effects six days after, a brief thirty-minute exposure to isoflurane in a rodent model of depression. In addition to revealing a prolonged anti-depressant effect, isoflurane is also reported to produce a rapid anti-depressant effect twelve hours after use (Antila et al., 2017). These effects were attributed to rapid molecular events involving TrkB phosphorylation and downstream signaling that is implicated in classical anti-depressant responses. Similarly, anxiolytic effects of the inhalational anaesthetic sevoflurane were observed in a model of post-surgical pain when administered coincidently with a formalin injection. The therapeutic anxiolytic effects were specific to the inhalational anaesthetic sevoflurane, with no inhibition of anxiety-like behaviours apparent when treated with the intravenous anaesthetics propofol or pentobarbital sodium (Luo et al., 2015). Taken together, there is evidence for both a therapeutic role for inhalational anaesthetics on the adult brain, as well as the potential for long-term detrimental effects. The powerful role general anaesthetics can have on modulating brain function in both the short term and long term is a great topic of interest and concern.

An overlooked aspect of general anaesthesia on brain function is its potential to cause neuroinflammation. Preclinical studies in the young and aged rodent brain have revealed an association between general anaesthetic exposure and cognitive impairment. In the young and aged brain pro-inflammatory cytokines in both neurons and glia have been associated with volatile anaesthetics sevoflurane and isoflurane. In contrast, intravenous anaesthetic propofol does not exert a pro-inflammatory response and may even attenuate neuroinflammation (Vutskits and Xie, 2016). The recognition of general anaesthetics as potential contributors to neuroinflammatory responses is an interesting, and potentially confounding facet in the study of experimental pain and injury. This is particularly so with the advent of emerging preclinical data revealing an important role for the signalling of pro-inflammatory mediators on disrupting affective behaviours in different pain states (Fiore and Austin, 2016). These data suggest that general anaesthesia may be exerting previously unnoticed acute and

sustained effects on the adult brain by itself and in combination with surgery and its associated stressors.

In light of emerging data, the implications suggest a cautious approach in interpreting experimental data derived from experiments that require the use of inhalational anaesthetics. Of particular intrigue are the subtle effects that general anaesthetics appear to have on behavioural outcomes. These appear to be species specific, anaesthetic specific and dependent on the duration of anaesthetic exposure. These subtle influences are detailed in a study by Yonezaki and colleagues (2015) who systematically characterized the post-anaesthetic effects of differing concentrations of isoflurane, long after initial exposure, on a range of behavioural tests including, sensory, motor, emotional and cognitive behaviours. The authors call attention to the different post-anaesthetic behavioural effects in rats and mice reported by others (Uchimoto et al., 2014) concluding that a cautious approach in interpreting the effects of post-anaesthetic behavioural outcomes must be taken.

This call for caution may be a particular concern for experiments that require long exposures to inhalational anaesthesia, such as neuroanatomical studies that subsequently investigate behavioural outcomes. Prolonged exposure to isoflurane (2–4 hours) resulted in prolonged neuroinflammation and impairments in cognitive behaviours that were indistinguishable from cognitive dysfunction that resulted from surgery involving an incision of the abdominal wall (Callaway et al., 2016). In contrast, twenty-minute exposure to isoflurane did not produce cognitive impairments, but peripheral surgery under isoflurane produced prolonged cognitive impairments and increased neuroinflammation in mice (Cibelli et al., 2010).

Similarly, in rats the effects of twenty-minute exposure to halothane anaesthesia did not produce any alterations in social behaviours, but when combined with nerve injury impairments in social behaviours were observed (Kang et al., 2017). Despite no changes in behavioural measures a large and enduring increase in BDNF and TrkB mRNA were detected in the prefrontal cortex six days post-anaesthetic exposure, but changes were absent in rats that received surgery (incision of skin and fascia of the hindlimb), and surgery with nerve injury. Even when not eliciting a measurable alteration in behavioural output inhalational anaesthetics are modifying the neuronal circuit of the adult brain in an enduring and previously unforeseen manner. These observations make the study of general anaesthesia on brain function an exciting avenue of experimental research.

However, a problem in the study of general anaesthesia in animal models and brain function is that the majority of experiments are performed independently of the presence of surgery or of other acute stressors that are often encountered in the perioperative period. A situation rarely encountered with humans. This is an important issue as the adult brain is vulnerable to the effects of peripheral surgery, which has been shown to result in neuroinflammation related cognitive impairments in mice, that were not observed with a short exposure to isoflurane anaesthesia alone (Cibelli et al., 2010). Alternatively, the use of animal models to study the influence pain and injury have on brain function closely mimics the surgical conditions encountered by humans, including the acute stressors encountered often in the perioperative period. In the experimental context, the ability to study the long-term effects of pain and/or injury independently of anaesthesia and surgery is unethical and impractical. When considered together it can be seen that general anaesthetics by themselves and in combination with surgery are having a role in altering brain function and behaviour. The degree that general anaesthetics contribute to shifting the overall outcomes for better or for worse is an interesting and important question.

The implications are intriguing both in the context of therapeutics and experimental design, execution and data interpretation. Both the rapid and long-term effects of inhalational anaesthetics suggest an interesting and promising role in the modulation of the adult brain function in psychiatric diseases. For the scientific community, inhalational anaesthetics form a crucial component of experimental research. In particular, in investigating the role of brain function and behaviour. To avoid confounding factors raised by the potential long-term physiological, biochemical and behavioural effects of general anaesthesia these effects should be taken into account when interpreting experimental data.

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